

THE
EXTRA PHARMACOPŒIA

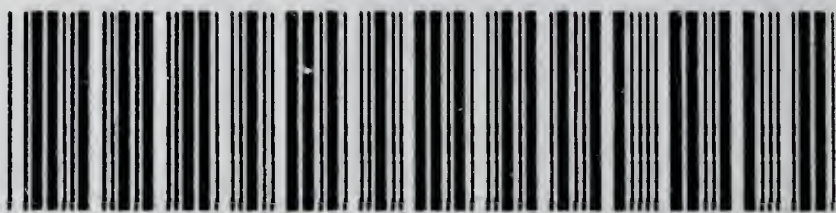
MARTINDALE
AND
WESTCOTT

VOL. II

TWENTIETH EDITION

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THE EXTRA PHARMACOPCEIA

OF
MARTINDALE & WESTCOTT

•
TWENTIETH EDITION
VOLUME II



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VOLUME II

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PREFACE

On April 8th, 1933, WILLIAM HARRISON MARTINDALE, son of the WILLIAM MARTINDALE who first produced the "Extra Pharmacopœia" in 1883, died. There can be little doubt that the intense personal attention and application devoted by him to the yearly increasing task of revision of the book contributed to his death. It was an event which deprived pharmacy and medicine of a personality notable yet personally little known outside a limited circle and it raised immediately the question, "What is to become of the 'Extra Pharmacopœia'?"

Martindale's "Extra Pharmacopœia" had owed much to the self-sacrificing personal labours of William Martindale and of W. H. Martindale (aided for a period by DR. WESTCOTT) in reducing to order and to a manageable compass references to the outstanding original work and the notable advances throughout the whole field of therapeutics. They had animated the whole work with an indefinable personality which expressed itself at times in *ex cathedra* judgments of a refreshing directness and at others in the warnings of an experienced and well-informed mind against the stampede of novelty. The careful application of a team of revisers might provide the first ingredient; the second was probably incapable of recapture. What was clear was that the "Extra Pharmacopœia," by virtue of the wide range of its contents and the comprehensiveness of its references to the literature, had met a need in medicine and in pharmacy and that if it were to be neglected, both sciences would be the poorer. Moreover, the rapid expansion of the medical sciences in recent years and the vast increase in the bulk of the scientific literature to be examined had made the continuance of revision by one individual an impossibility and pointed clearly to the work being undertaken by some organisation having medical, pharmaceutical and chemical experts available, preferably an organisation having no direct commercial interests.

It was in these circumstances that the Council of the Pharmaceutical Society of Great Britain decided that it was desirable to take over the responsibility for the continued production of Martindale's "Extra Pharmacopœia," and negotiations for its purchase from Dr. Martindale's executors were concluded in December 1933. The responsibility for its revision was delegated by the Council to the British Pharmaceutical Codex Revision Committee and Mr. C. E. Corfield, the Editor of the Codex, was appointed Editor of "Martindale." This arrangement has not only facilitated revision but has ensured that the two books shall be complementary. Dr. Martindale's illness

and the lapse of time between his death and the taking over of the book by the Society have led to some delay in the revision and this second volume of the 20th Edition, which should have been published in 1933 according to a long-established time-table, is not, in fact, available until the autumn of 1935. Nevertheless, the machinery of revision is now such as to ensure the regular production of future volumes. Experience may show that considerable changes in content are called for in a book which has been built up gradually over many years without sweeping and comprehensive revisions. Nevertheless, should such changes be needed they will be introduced gradually and with the remembrance that the present form of the book has stood the test of time and is familiar to users.

The first volume of this Edition is devoted mainly to treatment with drugs and chemicals, and this volume, like its predecessor is concerned with matters of diagnosis, analysis and assay of medicinal products and divers subjects associated with medicinal chemistry and pharmacy which could not be included in the first volume. A large proportion of the matter has been completely rewritten and the whole of the book has been submitted to a detailed and exhaustive examination with the object of removing information no longer considered of value to medical practitioners, pharmacists and analysts and replacing it by more useful accounts and researches concerning modern substances used in the treatment of disease.

Analytical Addenda

The section relating to the analytical notes on the chemicals and materia medica of Volume I has, for all practical purposes, been entirely rewritten, and the miscellaneous notes which frequently had no connection with this aspect of the subject, have been replaced by an up-to-date précis of information of general interest to the supplier and user of modern medicinal substances.

Care has been taken, as far as possible, to avoid confusion between the two volumes, and the reader is here reminded that, in general, information on the manufacture, composition and therapeutic uses of individual compounds and preparations appears in Volume I and that in this volume notes on these subjects are added only when recent advances necessitate their inclusion in order to supplement and complete the information contained in the first volume.

Greater emphasis and attention is now given to the importance of the newer methods of control resulting from the recent complete revisions of the *British Pharmacopœia* and the *British Pharmaceutical Codex*. The revision of these two authorities has brought about a critical review of older methods and has established approved and tested methods, many of which are new and, therefore, justify special mention. The scheme includes notes and comments on all the more important standardised substances of the *British Pharmacopœia* and the *British Pharmaceutical Codex*.

and they are arranged in groups in a manner which will assist the reader in making comparisons between substances of similar nature. More recent comments and criticisms are inserted, and the reader is thus provided with the most up-to-date information in this branch of the subject.

Attention has also been given to corresponding substances in the *principal foreign pharmacopæias* and, therefore, the methods in use in different parts of the British Empire are compared with those used for similar substances in the pharmacopæias and official formularies of America, Europe, Japan and other parts of the world. It is frequently of interest and value to have information showing the chief differences in composition and methods by which the purity of a substance is controlled in different countries, and these notes will be of special value from that point of view alone.

The work done by the BRITISH STANDARDS INSTITUTION in formulating agreed specifications for material used in various industries has proved of immense value. Specifications are available for many industrial chemical substances, and manufacturers and buyers who take advantage of their usefulness have solved many of the problems which previously have arisen on account of the variations resulting from the lack of uniformity in composition or methods of standardisation. Reference is made in these pages to the existing specifications for substances of pharmaceutical interest including those for various phenols and solvents.

References are made to some of the definitions and standards for food products which have been adopted by the UNITED STATES DEPARTMENT OF AGRICULTURE for enforcing the food and drugs acts. These definitions and standards include many articles which are described in the *British Pharmacopæia* and *British Pharmaceutical Codex* and because they differ in many important respects from the official British standards for the corresponding drugs, comparison in many cases should be of practical value.

The sections dealing with *hormones and glandular products* have been very much extended in accordance with the recent development in their use. The testing of many of these substances has been investigated by the Permanent Commission on Biological Standardisation of the Health Organisation of the League of Nations, and International Standards have been recommended and prepared. An account of these standards and of methods of estimating preparations of the different hormones by comparing them with these standards is given in sufficient detail to make the procedure clear. Not only are those substances discussed which are already official in *B.P.* '32, such as thyroid, pituitary (posterior lobe) extract, and insulin, but the newer hormones are also treated. Thus the hormones of the anterior lobe of the pituitary including the gonadotropic hormone, the ovulation-producing substance, the thyrotropic hormone, the so-called male and female hormones (the latter more commonly known as œstrone), and the hormone

of the corpus luteum, progesterin, are fully considered. The list also includes parathyroid extract, and extract of suprarenal cortex.

The following are a few of the many important points that are dealt with in this section:—

ACIDUM GLYCEROPHOSPHORICUM. The new standards of the *British Pharmaceutical Codex* for glycerophosphoric acid and the glycerophosphates of calcium, iron, magnesium, manganese, sodium and potassium and the revised processes for their determination. Some variation in composition occurs in the salts of commerce, and it is believed that these new definitions will give greater uniformity in the preparations containing them.

ACIDUM HYDROBROMICUM. The requirements of the *British Pharmaceutical Codex* for a concentrated hydrobromic acid will be of assistance in the preparation of the official dilute acid and bring this preparation into line with hydrochloric acid. Attention is given to the new limit test for chlorides in the medicinal bromides and to the importance of the new official method for the direct determination of iodine in iodides. These methods have formerly not received sufficient attention in text-books and standard reference books on analytical chemistry, and their applications to the analysis of mixed halides have not received the attention which they deserve.

ACONITE. The chemical assay for ether-soluble alkaloid of the *British Pharmacopæia*, 1914, is not now used for the root of the *British Pharmacopæia*, 1932, or for the tincture now included in the *British Pharmaceutical Codex*, and it is stated that some variation in the activity of different supplies will arise in consequence. Although the chemical test still has its supporters, a toxicity test on mice is advocated in which samples of the tincture are compared with a standard prepared from a series of ten samples of dried and powdered root.

ACRIFLAVINE. Recent work on the composition of this powerful antiseptic shows that it is a mixture of compounds. The results of analyses of some commercial flavines are included, and tests for purity and methods of assay are described. Proflavine and euflavine are official in the *British Pharmaceutical Codex*.

ADRENALINE. Although not required in any of the pharmacopœias, biological tests for adrenaline are often applied. Descriptions are given of the methods based upon its effect on the blood pressure of the spinal cat and on a strip of the isolated intestine of the rabbit suspended in Ringer's solution. The biological method used for the assay of suprarenal cortex is described, and mention is made of the recently isolated hormone, cortin.

ANTIMONY. Outbreaks of poisoning due to drinking lemonade prepared in enamel vessels have been noted, and the total prohibition of antimony in hollow-ware articles used for preparing food is advocated. Appreciable amounts of boron and fluorine in the enamel on iron-ware have also been found and the exclusion of constituents containing them may be desirable.

ARSENIC. The section on arsenic contains a useful summary of the requirements for the organic arsenic compounds including notes on the chemical and biological tests. Tryparsone is the *B.P.C.* name for the arsenical now used in the treatment of neurosyphilis and known as Tryparsamide.

BATTISTE. A summary is given of the new requirements for protectives, including battiste, jaconet, oiled silk and oiled cambric. The difficulties arising from the use of inferior products are expected to disappear when these revised products of the *British Pharmaceutical Codex*, 1934, have become established.

CINCHONA. Notes on the composition of the numerous cinchona products include references to quinetum and totaquine introduced by the Malaria Commission of the League of Nations and recommended for use instead of cinchona febrifuge which has been shown to be frequently of very inferior composition. Reference is made to the different hydrated forms of quinine sulphate official in different countries and the various ways of examining this salt for the absence of other cinchona alkaloids. The composition of the very large number of quinine salts in the *B.P.* and the *B.P.C.* is summarised by means of a table from which their activities can be compared by reference to the figures for their alkaloid content. An account is also given of the biological test used for determining the value of the numerous antimalarial remedies recently introduced.

CRESOL. The various cresols available for the preparation of lysol are described and a simplified assay process for the latter is included.

DIGITALIS. Full information is given on the recent advances in the chemistry and standardisation of digitalis leaf and its preparations. The biological assays described include the frog method, the cat method, the guinea-pig method, the pigeon method, and their application in the official pharmacopœial processes. References are retained to the chemical method used by the late Dr. Martindale, but preference is now given to the biological processes which have withstood the critical tests to which they have been submitted before being given pharmacopœial recognition. The new *B.P.C.* Digitalin is of interest, as well as the new crystalline glycoside Digoxin manufactured from the leaves of *Digitalis lanata*.

ERGOT. The composition and standardisation of ergot preparations continue to receive the undivided attention of both chemist and pharmacologist. The pharmacopœial colorimetric method based on the ergotoxine content of the drug is described, as well as the cock's comb assay process of the *U.S.P.* and the rabbit uterus method introduced by Broom and Clark. The observations of Chassar Moir on the activity of the *B.P.* 1914 extracts in stimulating the puerperal uterus indicated the presence of an active constituent other than ergotoxine, and reference is made to the recent isolation of the new alkaloid, named ergometrine, by Dudley and Chassar Moir.

EXTRACTUM MALTI. A summary is included of the grade designations and definitions of malt extracts produced from barley grown in England. The requirements are given for pharmaceutical, bakers' and veterinary malt extracts, and the particular methods to be employed for the determination of diastatic activity, etc.

EXTRACTUM PITUITARII. The biological methods by which the potency of pituitary (posterior lobe) extract can be determined by its stimulant action on the isolated uterus of the guinea-pig, by its pressor action on the blood pressure of the spinal cat and by its antidiuretic effect on rats are described. In connection with the anterior lobe, methods are outlined for the quantitative estimation of the gonadotropic, thyrotropic and growth hormones.

FERRUM. The requirements for the various official compounds of iron are summarised, and references are made to the determination of traces of lead and copper. Lead may occur in appreciable amount in some official iron compounds, and in *Liquor Ferri Perchloridi Fortis* and some other preparations of the *B.P.C.* this impurity is limited to 50 parts per million.

GLYCERIN. Some continental pharmacopœias include a glycerin containing 12% to 16% of water. The methods for the determination of nitroglycerin in solution and tablets are described.

GOSSYPIUM. Attention is given to the important new and revised specifications of the *B.P.C.* for cotton wool, lint and gauze and the various medicated and other surgical dressings.

HYDRARGYRUM. The methods for the control of mercury compounds and preparations have received careful consideration at the hands of Pharmacopœia and Codex committees, and notes on these methods as well as more recent ones are given. Several of the methods given show considerable advantages over the older ones, and many of the difficulties experienced by analysts in the examination of ointments containing mercury compounds may be removed by the adoption of some of the new processes. Solution tablets of mercuric iodide are now standardised on their mercuric iodide content, and mercurochrome when used for intravenous injection should comply with a test for toxicity.

HYOSCYAMUS. It should be noted that in some countries galenical preparations, including the extract and tincture, are prepared with *Hyoscyamus muticus* containing not less than 0·8% of alkaloid instead of from *H. niger* containing 0·05%.

IODINE. The iodised oils employed in X-ray work are still mainly of a proprietary character and little appears to have been done to produce standardised preparations of published composition. Useful notes are included on the official and unofficial methods for the determination of the iodine values of oils and fats. Processes for the determination of iodine in biological substances have been investigated by the Medical Research Council and a method has been evolved by C. O. Harvey (*Spec. Rep. Ser. med. Res. Coun., Lond., 1935, No. 201*) which yields consistent results in the hands of different workers.

LIGAMENTA. Under this heading a general account is included of the new and revised specifications for bandages. These specifications are in force for National Health Insurance purposes and samples are examined periodically at the Testing House of the Manchester Chamber of Commerce.

OESTRINUM. The biological test for the standardisation of the œstrus-producing hormones and the International Standard œstrone are described. The estimation of progestin in extracts of corpus luteum and the biological methods for determining the potency of the testicular hormones by the cock's comb and rat tests are also included.

OILS—VOLATILE AND FIXED. The particulars concerning the composition of the various commercial varieties of the essential oils and the references to the methods by which both essential and fixed oils are examined have been completely revised. The term "terpeneless" now generally implies an oil which has been obtained by fractionation and is free from both terpenes and sesquiterpenes, and in consequence the tables have been revised. The new pages contain a much more complete account of the various oils either under the medicinal substances from which they are obtained or in a convenient alphabetical order under *Olea Essentialia* and *Olea Expressa*. The subject of cod-liver oil and its vitamin A and D potencies has been rewritten in the light of recent knowledge concerning methods of chemical and biological standardisation, and attention has also been given to the vitamin content of fish-liver oils other than cod, including the much discussed halibut-liver oil.

OPIUM. Some defects in the International Process of the Commission of Experts for the Standardisation of Methods for Determining the Morphine Content of Raw Opium are outlined. Of the published methods, that of the *British Pharmacopœia* is preferred. The notes include the newer and more satisfactory processes for determining morphine in galenical preparations and small amounts of morphine in other opium alkaloids. The different varieties and numerous constituents receive full consideration.

PHENOL. The available specifications for different grades of carbolic acid are referred to, and the methods for determining phenol in medicinal preparations are described.

RHUBARB. References are made to the detection of adulteration in powdered rhubarb including the methods used in the examination for rhapontic rhubarb.

STROPHANTHIN. The standardisation of strophanthin and tincture of strophanthus is described, together with up-to-date information regarding the activities of ouabain and other strophanthus glycosides. Biological standardisation is generally adopted but chemical methods still appear in some pharmacopœias.

THYROID. The recommendations relating to the iodine content are described and the biological methods of assay based upon the resistance of mice to the action of acetonitrile, the oxygen consumption of guinea-pigs or its effect in causing loss of body weight

in guinea-pigs are outlined. The effect of parathyroid extract on urinary calcium as a means of controlling the potency of this extract is also described.

Recognition of Organic Chemicals

Comparatively few alterations have been found necessary in the systematic scheme for the recognition of organic medicinal substances, but the table of corroborative tests has been modified in certain respects and extended. The nomenclature of the substances included is now in accordance with that adopted in the *B.P.* 1932 and the *B.P.C.* 1934. Many new special tests are given and numerous substances now in common use have been added to the table. Among the latter may be mentioned arecoline hydrobromide, berberine sulphate, betanaphthol, caffeine and sodium benzoate, calcium sodium lactate, cinchonidine sulphate, digitalin, ergotoxine, euflavine, iodophthalein, quinine ethyl carbonate, quinidine, silver proteinate and sodium aminarsonate.

Sensitive Organic Reagents

Following on the researches of Prof. Feigl, considerable prominence has been given in recent years to the use of complex organic chemicals in the detection and estimation of traces of metallic and other radicles. Owing to their very high sensitivity the principal difficulty in applying these reagents is that of ensuring that the conditions of the test preclude the possibility of any interference of ions other than that for which the reagent is being used. Reagents are available for detecting the majority of inorganic radicles, and the methods of applying them so as to ensure specificity are described in detail. Directions are given for the use of some of the reagents in quantitative analysis.

Indicators

The table of indicators has been enlarged by the insertion of alkali blue, bromocresol green, cresol red, dimethyl yellow and phenol violet, all of which are included in the *B.P.* 1932. In several cases the method given for the preparation of a solution of the indicator has been altered so as to correspond with that of the pharmacopœia and practical notes have been incorporated to indicate any special properties or uses.

In addition to the indicators included in the table, which are those most frequently used in volumetric analysis, other types are available and are often useful for particular purposes. Details are given of mixed indicators, of the use of umbelliferone and quinine as fluorescent indicators, of several substances, chiefly fluorescein compounds, as adsorption indicators, and of diphenylamine as an oxidation-reduction indicator.

Analytic Quartz Lamps

Increasing attention is being paid to the use of fluorescence in ultra-violet light as a means of qualitative analysis. This method of investigation is particularly useful for the detection of adulteration and is therefore a useful aid to the examination of drugs, especially those containing alkaloidal constituents. The colours.

of the fluorescence obtained with a large number of alkaloids are described, and also the results obtained with liquid extracts and tinctures by the so-called capillary method.

Analysis of Urine, Blood, etc.

The chapters on the Analysis of Urine, Blood, Fæces, Cerebro-spinal Fluid, etc., have been drastically revised and the various sections almost entirely rewritten. As far as possible, a selection is given of the methods in constant use in the London hospitals, with an indication of the value of the various tests in certain pathological conditions. The introduction of many excellent micro-methods of blood analysis has necessitated the elimination of some of the older and more cumbersome procedures. The section dealing with hæmatology has been critically revised and as far as possible useful methods and accepted views summarised. In view of the greatly extended use of blood transfusion a section on the methods of blood grouping has been added. More attention has been given to the determination of the size of red blood cells and to conditions found in the various hæmorrhagic diseases.

Nutrition and Vitamins

The matter contained in the former edition under Nutrimenta has been examined critically and the changes made, owing to rapid and important advances, are somewhat considerable. This section deals with some general questions concerning nutrition and the vitamins, including their chemistry, estimation, and the more recent investigations regarding their uses in therapeutics.

The most important work on nutrition published within the last five years includes:—

- (a) A reconsideration of the calorie requirements of man at different ages under different conditions of living, by the Nutrition Committee of the British Medical Association and the Nutrition Advisory Committee of the Ministry of Health;
- (b) The isolation of at least four vitamins in a very nearly pure, if not quite pure, state, and the synthesis of one of them;
- (c) The recognition of the existence of several new vitamins;
- (d) The adoption for international use of standards of reference for the estimation of the four vitamins A, B₁, C and D;
- (e) Some carefully controlled work on the clinical use of vitamin preparations more nearly pure than had hitherto been available.

In particular, a formula has been proposed, with a good deal of evidence in its favour, for the constitution of the molecule of vitamin A. Its formation from carotene in the animal body has stimulated research on the lipochromes with the result that, so far, four substances with vitamin A activity are known, viz., vitamin A itself, α -carotene, β -carotene and kryptoxanthin. An empirical formula for vitamin B₂ has been worked out. Ascorbic acid has been identified as vitamin C and not only has it been analysed but synthesised also. Calciferol has been identified as vitamin D and is regarded as an isomer of ergosterol. Fresh workers on vitamin E have confirmed most of the early findings and added important new knowledge which indicates that vitamin E is closely related to the sterols or to the amyryns. The possible identity of

vitamin B₂ with one of the flavins has stimulated research on the lyochromes.

Other vitamins which are now generally recognised are vitamins B₃, B₄, B₅, B₆, factor γ , and a "casein factor" which may be identical with a substance called physin prepared from liver. The existence of other factors also is suspected.

The adoption of standards of reference for the estimation of vitamins A, B₁, C, and D has made it possible for workers in all parts of the world to state their results in International Units, provided the standards are used properly. It is essential to make a test on the standard simultaneously with every estimation of the vitamin content of a substance, and it is quite wrong to determine the effect of a dose or doses of the standard on a stock of rats at one time only and then to compare with this a dose or doses which produced similar results at another time. A stock of rats varies from time to time and the difference in sensitivity can only be measured and allowed for by testing the standard whenever a test of any substance is made.

The "blue value" of a sample of cod-liver oil (i.e., the intensity of the blue colour developed on treating the oil with antimony trichloride) is now regarded as being useful only for sorting oils into "good, bad, and indifferent." Of two oils having blue values of 10, one may have a vitamin A value as much as four times that of the other. If the blue value is determined on the unsaponifiable fraction of the oil, better agreement is obtained with the biological value. The intensity of absorption at 328m μ of cod-liver oil itself is regarded as a truer measure of the vitamin A value than is the blue value, but this also should be measured on the unsaponifiable fraction of the oil.

The influence of vitamin D on the structure of the teeth is becoming more and more widely recognised; the investigations of the nervous lesions induced by a deficiency of vitamin A are opening a limitless field of research, while the fuller knowledge of the B vitamins promises, among other things, to solve the long-debated question as to the ætiology of pellagra. Vitamin E concentrates have been used successfully for human beings as well as for cows, sheep, pigs, hens, and rats.

Milk

The ordinary methods of chemical analysis and examination of milk are described as in the previous edition with certain modifications and additions. Tables are given showing the average composition of cow's milk and of milk from other sources. Variations in composition and the chief causes from which deficiency may arise are discussed.

The FREEZING-POINT TEST has come into great prominence in recent years as a means of distinguishing between samples which have been adulterated by the addition of water and abnormal samples. Much evidence has now been accumulated of the definite value of the test for the purpose, but it must be carried out on practically fresh milk. The removal of fat and the addition of

separated milk do not affect the freezing-point. Owing to the low standards for solids-not-fat adopted by the Board of Agriculture, the full extent to which milk has been watered is not usually indicated by a calculation based on the solids-not-fat figure. A freezing-point determination furnishes perhaps a truer measure of the adulteration, and the adoption of this test in New Zealand has resulted in a general rise in standard of the milk supply of a town or district, which is at once evidence of systematic watering in the past and indubitable proof of the value of the test.

It is, however, another and larger aspect of the "Milk Problem" which has been and continues to be stressed in these pages, viz., the provision of milk which is pure chemically and bacteriologically, derived from disease-free herds, produced and conveyed from farm to consumer under clean hygienic conditions.

PASTEURISATION as a means of ensuring a "safe" supply is very strongly advocated, and although it is generally agreed that there is some impairment of the food-value of the milk, it seems to be largely held that the effect is slight and easily remedied by suitable additions to the diet. Even in the case of Grade A (T.T.) Milk it is often pointed out that if it can be guaranteed tubercle-free there are other most undesirable organisms which are frequently present. To many, therefore, it appears that for years to come the most reliable milk supply that can be looked for is a "tuberculin-tested" milk which has also been subjected to pasteurisation.

The attainment of a Grade A standard for the general supply is confidently hoped for as a result of the "Accredited" Milk Scheme which came into force in May, 1935. Side by side with this scheme we have the *Tuberculosis (Attested Herds) Scheme*, which is far more drastic in its requirements for the reason that it aims at the complete eradication of tuberculosis from herds in England and Wales. Progress to such a point must necessarily be slow, and success can only be achieved by the most thorough and searching methods. The above schemes are described in some detail and their importance can scarcely be exaggerated. The health of the nation in great measure depends on the right solution of this problem, which affects the youngest generation most. On these grounds the heaviest expenditure is justified on efforts at all likely to be successful in raising the standard of health.

The Ministry of Health instructions for the bacteriological examination of milk produced under the Special Designations Order are given in full, as it is important that the technique should be strictly adhered to for comparable results.

Cream

The article on cream has been revised and extended to include official regulations, suggested standards and methods of examination. A formula is given for the calculation of added water, based on the determination of the freezing-point of the sample. Standards for fat in this substance have been strongly advocated by the Council of Agriculture, and are surely overdue.

The composition and preparation of ARTIFICIAL CREAM are discussed, and references given to prosecutions and convictions under the ARTIFICIAL CREAM ACT. Under ICE CREAM will be found tabulated results of the bacteriological examination of samples taken in a London district during the summer of 1934.

The main features of the Rules and Regulations applying to CONDENSED MILK and DRIED MILK are set forth and followed in each case by detailed methods for the chemical examination of these products, and the calculation of the "equivalent points" represented by the contents of the containers.

Butter

Some account is given of the composition of butter-fat and its adulterants, and the Reichert-Polenski and Kirschner processes are explained and directions given for carrying them out.

Jam

The adoption of standards for jam by the Food Manufacturers' Federation in consultation with the Society of Public Analysts, and the establishment under the National Mark Scheme of superior quality preserves made from fresh fruit, have served to stimulate research on the constituents of fruit and fruit pulp to provide data for the determination of the proportions of fruit used in preparing the jams, jellies, etc. Special analytical methods have been published, accompanied by tables, showing the results obtained with different fruits. Methods of examination applied to jam have been evolved, and an account of them is given in this edition together with details of the standards prescribed. Tests are also given for the detection and determination of preservatives, and for controlling the addition of substances for the purpose of "improving" the article, and producing a satisfactory set.

The establishment of superior quality preserves under the National Mark Scheme is directly designed to encourage the use of home-grown fruit, and similar schemes embrace other home products such as honey, cider, bottled and canned fruits and vegetables, which are required to be of high quality and to conform to the standards prescribed.

Vinegar

A brief account of the manufacture of vinegar and the different varieties produced in this and other countries is accompanied by a description of the forms of adulteration practised, and of the methods of examination. The Local Government Board definitions and recommendations with regard to vinegar are supplemented by those of the Society of Public Analysts and the Maltese Vinegar Brewers' Federation.

Water Analysis

This section has been completely rewritten, and the whole is now in accord with modern practice. Space considerations have made it necessary to leave out the more controversial matter, but a reference to the previous edition makes the information omitted readily available.

The supply of potable water for domestic purposes is of the utmost importance and has a direct bearing upon the health of the community, but the information regarding the chemical and bacteriological control of these supplies is restricted to a few specialists. It is the object of this chapter to make this information available to a wider public in a form which can be appreciated by the non-specialist. Thus the main physical, chemical and bacteriological tests, by which the purity of our water supplies is ensured, are outlined in sufficient detail to enable the fundamental principles to be grasped.

Some attempt has been made to indicate the inferences to be drawn from analytical reports, but the reader is warned that such inferences are more a matter of experience than precept. The review of the annual reports of the Metropolitan Water Board has been condensed so that the main conclusions are thrown into relief. Although the reports refer chiefly to London water, the findings are generally applicable and extremely valuable owing to the very large number of samples concerned.

Chemotherapy

The section previously called "synthetic notes" has been re-written under the title of Chemotherapy. The difficult task of endeavouring to present a general survey of this field within the compass of a few pages has been attempted and, whilst no claim for completeness is made, it is hoped that the main object has been achieved. The most important of the many theories proposed to relate therapeutic action with either chemical constitution or physical properties are outlined, together with the effects of stereoisomerism and metabolic reactions.

Similarity of chemical constitution does not necessarily mean similarity of physiological action, nor is the contrary true, but the activity encountered in the various types of chemical compounds, and the effect of the introduction of functional groups into the molecule, are summarised. Several instances of the occurrence of peaks of activity in homologous series promote interesting speculations concerning the mode of action, and the same is true of the phenomenon of specificity. Although the alkaloids as a group exhibit few general relationships, their physiological activity has attracted many workers. Chemotherapeutical research amongst this group of natural products has led to the introduction into medicine of many new synthetic compounds. Examples are cited showing the genesis of a number of local anæsthetics, and the relations between Plasmoquin, Atebrin and quinine; Syntropin and atropine; Prostigmine and physostigmine.

Bacteriological and Clinical Notes

In this section a number of bacterial and parasitic diseases are discussed with special reference to their ætiology, diagnosis by laboratory methods, epidemiology, and in certain cases, treatment by appropriate antigens or by chemotherapy. The subject matter

has been extensively revised throughout and it has been necessary to omit many old references in order to accommodate the new matter. In this revision it has been possible to rearrange the data to permit more easy reference to related subjects.

The particulars relating to Diphtheria Antitoxin, Tetanus Antitoxin, Antidysentery Serum and Schick Test Toxin have been brought into line with the specifications of the *British Pharmacopœia*, 1932, and in other cases where standards for international use have been adopted by the Committee on Biological Standardisation of the League of Nations, these have been noted.

Among the more important of the new contributions from a voluminous literature the following may be noted:—

ACTINOMYCOSIS. Modern workers ascribe this disease to *Actinomyces bovis*, and consider that infection takes place from the alimentary tract; this organism is present in the tonsils and in carious teeth of healthy persons. According to one observer, however, primary actinomycosis is rare, and the presence of *B. actinomycetum comitans* is diagnostic. In actinomycosis of the tongue treatment with X-rays or radium, together with fairly large doses of potassium iodide, following excision and primary closure is said to result, practically always, in a permanent cure.

ANKYLOSTOMIASIS. Several papers dealing with the value of hexyl-resorcinol in treatment are referred to.

APPENDICITIS. A diagnostic test employing atropine 1/100 grain hypodermically or by mouth is described.

BERI-BERI. The information given in previous editions concerning the incidence of beri-beri in India and its relationship to the diet of polished rice has not been repeated. The fact that this disease is primarily due to a deficiency of vitamin B is accepted by many workers, but bacterial agencies continue to engage attention, and a paper ascribing the causation of this disease to a gram-negative motile organism, the *Bacillus beri-beri*, is noted, and further work on the *Bacillus asthenogenes* shows this organism to exist in two forms, one of which is anaerobic and pathogenic in the absence of vitamin B.

BLACKWATER FEVER. The view is expressed that the last 20 years have seen no improvement in the methods available for the treatment of this manifestation of infection with malignant tertian malaria.

COCCIDIOIDES (CALIFORNIAN DISEASE). An infection closely resembling blastomycosis, caused by a mould belonging to the group of oidia frequently affects the lungs, and simulates pulmonary tuberculosis with fatal issue.

BOTULISM. Bacterial food poisoning is now a compulsorily notifiable disease in London.

CANCER. The whole of the matter in this section has been rearranged, and many of the abstracts of reports by various cancer research organisations have not been retained in this edition.

It has been shown that the constituent of tar having carcinogenic properties is 1 : 2 benzpyrene, and a synthetic compound, dibenz-anthracene, is equally a powerful carcinogenic agent when applied to the skin of mice.

The Bendien test based on flocculation of the patient's serum when it is mixed with sodium vanadate and acetic acid has been investigated, but its validity for the diagnosis of cancer has not been confirmed; other papers describe various modifications of the original reaction of which details are given.

Test meals do not furnish evidence which is sufficiently definite for diagnosis, except for gastric carcinoma. Lactic acid has no specific relation to cancer of the stomach, but all patients in whom it can be demonstrated should be regarded as potential sufferers from gastric cancer until the contrary is proved.

Treatment of carcinoma with extracts of various tissues such as spleen, thymus, connective tissue and posterior pituitary is discussed in several papers, although the results are inconclusive. Injections of snake venom and of calcium gluconate have been used to relieve pain. A new sulphur-selenium colloid and a radio-active selenium colloid in which selenium is combined with feebly radio-active radium elements have been used intravenously with considerable benefit. Further work has shown that activated fluorescein has no influence on the value of radiations, although it has a slight antibacterial action which may turn the balance in the patient's favour.

CEREBROSPINAL FEVER. A positive complement fixation reaction occurs in at least 75% of cases of cerebrospinal fever, and is diagnostic in a case showing meningococcal symptoms. An increase in the incidence of cerebrospinal fever in England is recorded in the returns for the period 1929-32.

Details are given of a specimen ketogenic diet for the treatment of urinary infections, which is reviewed in a number of papers.

DIPHTHERIA. Two forms of the *Corynebacterium diphtheriæ* have been described—*gravis* and *mitis*. Although at first *gravis* was believed to be associated with severer forms of the disease and the *mitis* form with milder attacks, it has been shown that *mitis* strains are at least as virulent as *gravis* under laboratory conditions and have produced much better toxins.

Diagnosis from examinations of the direct smear from a properly taken throat swab is said to be satisfactory in patients under 18 years. Reactions from the use of diphtheria antitoxin are said to be increasing in frequency, amounting to 80% of cases in children and 95% in adults. Ephedrine by mouth is successful in aborting these reactions.

Active immunisation against diphtheria has produced a voluminous literature, of which only a small selection has been abstracted. The important observation is recorded that under certain conditions the number of virulent carriers may be increased, especially when active immunisation is only partially carried out in a community. Toxin-antitoxin mixtures, although

still employed in America, have never been popular in Gt. Britain, where preparations of toxoid are more favoured.

Toxin-Antitoxin Floccules—or **Toxoid-Antitoxin Floccules**—are less prone than toxoid to produce reactions in hypersensitive persons. A method of immunising by a single injection of alum-precipitated toxoid is likely to be very popular if it can be shown to be no less effective than the three dose methods.

GAS-GANGRENE infections during pregnancy and the puerperium, observed in a number of cases at the Obstetrical Dept. of a large London hospital, suggest that gas-gangrene antitoxin should be given early in all cases when circumstances point to the probability of generalised infection.

INFLUENZA. An important contribution on the ætiology of epidemic influenza shows that this disease is caused primarily by a virus which probably facilitates invasion of the body by bacteria, giving rise to various complications.

ORIENTAL SORE. The view is advanced that tropical ulcer should be regarded as a calcium-deficiency disease, and treatment with intravenous injection of calcium chloride has given remarkable results in some 500 cases.

LEPROSY. A histamine skin test for diagnosis is described.

MEASLES. Further papers on the use of convalescent serum and adult immune serum for prophylaxis are noted, from which it appears that adult serum is a valuable prophylactic which can be used on a larger scale than human convalescent serum.

MEDITERRANEAN FEVER is not synonymous with undulant fever, but is a distinct entity, of which a description is given.

PELLAGRA. Considerable modification of this section has been made by omission of references to many of the older papers.

Aetiology is discussed with particular reference to vitamin B.

PNEUMONIA. Rapid methods for direct typing of the organism are described, and details of the standard for the serum prepared by Felton's method are given.

POLIOMYELITIS. Treatment with convalescent serum, immune serum and an antistreptococcus serum prepared by Rosenow, forms the subject of a number of papers which are abstracted.

SCARLET FEVER. Sources of error in the Dick Test are referred to. For active immunisation of Dick-positive patients 5 doses of streptococcus toxin (scarlatina) appear to be necessary.

STAPHYLOCOCCUS ANTITOXIN and **STAPHYLOCOCCUS TOXOID** have given good results in the treatment of staphylococcal infections.

STREPTOCOCCI. The work of the late Sir Frederick Andrewes on the classification of hæmolytic streptococci is referred to.

SYPHILIS. Details are given of the Kline precipitation reaction, and a description of the Wassermann reaction has also been added; in spite of various modifications the Wassermann reaction is still the most largely used diagnostic test, although the Kahn test is apparently more sensitive.

TRYPANOSOMIASIS. The superiority of the trivalent arsenic

(and antimony) compounds over pentavalent derivatives is discussed in relation to its bearing on states of arsenic resistance or antimony resistance. The possibility of prophylactic use of "Bayer 205" against infection by *T. rhodesiense* is discussed.

UNDULANT FEVER. The increasing number of cases recognised in Great Britain is noteworthy, and evidence is accumulating to show that latent and subclinical infection is not uncommon.

WEIL'S DISEASE. The occurrence of leptospiral infection among sewer labourers and workers engaged in the handling and cleansing of fish is recorded, with a suggestion for more widespread clinical and diagnostic examination to reveal the exact incidence. Details of an agglutination reaction are given.

WHOOPING COUGH. Importance attaches to cultural methods in relation to the antigenic capacity of vaccines prepared from the *Hæmophilus pertussis*.

YELLOW FEVER. The use of mouse-fixed virus and immune serum for prophylaxis among laboratory workers in this disease has so far given protection lasting 6 months or longer.

Sterilisation

The account of methods of sterilisation has been entirely rewritten in order to bring the subject into line with the developments which have occurred since the publication of the last edition. The *British Pharmacopœia*, 1932, for the first time, introduced sterilisation processes for all solutions intended for injection and for apparatus used in preparing them. In the case of sterilisation by filtration the product has to conform with tests for sterility both towards aerobic and anaerobic organisms. As might have been expected, the bacteriological problems involved in the sterilisation of many pharmaceutical solutions are different from those experienced in other bacteriological work, particularly where sera and vaccines are concerned. At the time of publication of the 1932 Pharmacopœia, pharmaceutical literature was sadly lacking in any reliable data bearing on these problems, but the introduction of official methods stimulated much research and many valuable contributions to the subject have been made by various workers. The official processes have been criticised, particularly the process of tyndallisation. This has been shown to be unreliable and, if adopted, should be followed by tests for sterility. The results of the findings of the various workers have been embodied in the accounts of the various processes.

Disinfectants

An account is given of the new standard Rideal-Walker Test for Disinfectants issued by the British Standards Institution. Since the introduction of the Rideal-Walker test in 1903 much confusion has arisen because of the many variations of the test which have been put forward by investigators. There is no doubt that this standardised test will finally dispose of any ambiguity in Rideal-Walker values, for it is certain to receive general adoption by both buyers and sellers of disinfectants.

Some account is given of the principles underlying the various types of disinfectants, but for the special bactericidal and bacteriostatic properties of a particular substance the reader is referred to Volume I where such information is provided.

Gas Poisoning

Unfortunately another war is not yet outside the bounds of possibility, and therefore this section has been extended to include the agents used in chemical warfare. These have been classified according to their principal effects and the physical, chemical and physiological properties of the various substances used are treated in some detail. Thus the symptoms of poisoning by such agencies are clearly defined and suitable methods of treatment suggested. Methods used in defence against gas and in the decontamination of affected areas are briefly outlined.

Such information should be made readily available although it is hoped that the need to apply it will not arise. However, certain of the substances treated, such as phosgene, hydrogen sulphide, ammonia, etc., are common risks associated with specific industries and hence this section should prove of value even in times of peace.

Modern Views on Atomic Structure

The extension of our knowledge, in very recent times, of the internal structure of the atom is rapidly changing the whole aspect of chemistry. As a result the conception of valency has altered beyond all recognition, and even the physiological activity of certain drugs is being ascribed to their electronic characteristics. It is no exaggeration to say that repercussions are felt in all branches of chemistry. Hence, the continuance of a short section on this subject requires no apology in a work of this character. This section covers briefly atomic structure, atomic numbers, isotopes, periodic law, and valency.

Radiology and Electrotherapy

The sections on Radiology and Electrology have been completely rewritten and brought thoroughly up to date. As the tendency in recent years has been for so much specialisation to occur within the speciality of Radiology itself, it has been deemed advisable to place the subdivisions of that section—Radium, X-ray Diagnosis, X-ray and Radium Therapy, Actinotherapy, and Electrotherapy—each in the hands of a specialist in his own branch. Great care has been taken to present the material in such a manner as to render it intelligible to those who are not acquainted with radiological terms, and it is hoped that its value has thereby been greatly increased.

Proprietary Medicines

The information given in previous editions of *The Extra Pharmacopœia* as to the composition of proprietary medicines was taken chiefly from particulars published in the *British Medical Journal* in 1907 *et seq.*, and issued by the British Medical Association in the books *Secret Remedies* (1909) and *More Secret Remedies* (1912). During the last 25 years, largely owing to the growth of advertising,

the trade in patent medicines has vastly increased both in quantity and variety, while many products which formerly were popular have ceased to be available.

Since the 19th Edn. of Vol. II was published full information has become available concerning the ingredients of numerous "patent" remedies owing to the practice of destamping. It is becoming increasingly common for manufacturers to disclose the composition of their products and to print on the packages a formal disclaimer of proprietary rights in the formula or method of preparation. When this is done the product is no longer a proprietary secret remedy, and is therefore not liable to patent medicine duty. At the same time, proprietary rights in the name are retained by registering it as a trade-mark. As a result of this procedure it has been possible to give the complete formulæ, as printed on the respective packages, of a large number of hitherto secret remedies. In addition, any available particulars are recorded as to the composition of medicines which are still supplied bearing a patent medicine stamp.

A brief historical summary is given also of the various efforts that have been made from time to time, so far unsuccessfully, to protect the public from the dangers of false or exaggerated therapeutic claims.

Poisons and Dangerous Drugs

The Pharmacy and Poisons Act, 1933, *inter alia*, provides for the preparation by the **Poisons Board** of a list of the substances which are to be treated as poisons for the purposes of the Act. This subject will receive full consideration when the recommendations of the Poisons Board have been approved by the Home Secretary and the new poison lists and rules come into force.

The Schedule of Poisons at present (1935) in force may soon become obsolete, and in consequence it has not been considered desirable to indicate whether any of the substances mentioned in this volume are poisons or come within Part I or Part II of this schedule. The schedule is printed in Volume I, p. 990, and the following are the only more recent amendments, being additions to Part I:—

- (a) Dinitrophenol; dinitrocresols; preparations containing dinitrophenols; preparations or admixtures containing dinitrocresols. (April 11, 1934.)
- (b) Phenylcinchoninic acid, its salts, its esters; derivatives of phenylcinchoninic acid, their salts, their esters; preparations and admixtures containing phenylcinchoninic acid, its salts, its esters; preparations and admixtures containing derivatives of phenylcinchoninic acid, their salts, their esters. (November 14, 1934.)

For the purposes of this volume it has not been considered necessary to indicate whether any of the substances included come within the provisions of the **Dangerous Drugs Regulations**. In addition to the control of raw and prepared opium, and of the manufacture and supply of methyilmorphine (codeine) and ethylmorphine (Statutory Rules and Orders, 1933, No. 1156)

the following compounds come within these regulations (see Section I, Dangerous Drugs Act, 1932):—

- (a) Medicinal opium;
- (b) Any extract or tincture of Indian hemp;
- (c) Morphine and its salts and diacetylmorphine (commonly known as diamorphine or heroin) and the other esters of morphine and their respective salts;
- (d) Cocaine (including synthetic cocaine) and ecgonine and their respective salts, and the esters of ecgonine and their respective salts;
- (e) Any solution or dilution of morphine or cocaine or their salts in an inert substance whether liquid or solid, containing any proportion of morphine or cocaine, and any preparation, admixture, extract or other substance (not being such a solution or dilution as aforesaid) containing not less than one-fifth per cent. of morphine or one-tenth per cent. of cocaine or of ecgonine;
- (f) Any preparation, admixture, extract or other substance containing any proportion of diacetylmorphine;
- (g) Dihydroxycodeinone, dihydrocodeinone, dihydromorphinone, acetyldihydrocodeinone, dihydromorphine, their esters and the salts of any of these substances and of their esters, morphine-N-oxide (commonly known as genomorphine), the morphine-N-oxide derivatives, and any other pentavalent nitrogen morphine derivatives;
- (h) Thebaine and its salts, and (with the exception of methyilmorphine commonly known as codeine, and ethylmorphine, commonly known as dionin, and their respective salts) benzylmorphine and the other ethers of morphine and their respective salts;
- (i) Any preparation, admixture, extract or other substance containing any proportion of any of the substances mentioned in paragraph (g) or in paragraph (h) of this subsection.

Metric Units of Volume

Much of the confusion resulting from metric units of volume being defined in terms of units of length as well as in terms of volume occupied by a specific weight of water, has been cleared up by a report issued by the Institute of Chemistry from the Joint Committee for the Standardisation of Scientific Glassware. The Committee recommended "that the recognised international metric units—the litre (l) and millilitre or thousandth part of the litre (ml.)—shall be used as the standard units of volume, and that standard volumetric glassware shall be graduated in terms of these units and marked 'ml.' instead of c.c." The Committee also stated that "the publication of all results in terms of millilitres would remove the uncertainty due to the term cubic centimetre being used sometimes correctly, sometimes as equivalent to the millilitre, and sometimes as the space occupied, under conditions not generally well defined, by a quantity of water which has an apparent weight in air of 1 gramme."

This system has now been adopted almost universally for calibrating volumetric glassware, and such glassware is marked with the abbreviation "ml." instead of "c.c." The *British Pharmacopœia*, 1932, and the *British Pharmaceutical Code*, 1934, have adopted the millilitre. In the latter the abbreviation "ml." is employed, whereas in the former the alternative "mil" is used for stating doses. In this second volume of the 20th Edition of the *Extra Pharmacopœia*, the practice of the first volume has been followed by continuing to use "Gm." and "Cc."

for expressing doses of medicinal substances, but in analytical processes and tests the abbreviation "g." recommended by the Chemical Society is used for gram or gramme, and the abbreviation "ml." for the millilitre in preference to Cc. or c.c. for cubic centimetre.

The general adoption of the millilitre (ml.) in preference to the cubic centimetre (c.c.) is considered to be highly desirable—Report on Metric Units of Volume (British Standards Institution, Victoria Street, S.W.1).

Acknowledgments

In this revision the fullest use has been made of scientific papers and abstracts published in chemical, pharmaceutical and medical journals and periodicals, and much attention has been given to the selection of matter judged to be of greatest value to the pharmacist, the analyst and the medical practitioner. Assistance of much value has also been obtained from several persons having special knowledge of and experience in the work of the different sections of the book, and the Council of the Pharmaceutical Society desire to record their indebtedness to all these helpers. They are indebted especially to the members of their laboratory and office staff and in particular to:—

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ABBREVIATIONS

The abbreviated titles of journals are those given in the *World List of Scientific Periodicals* (2nd Ed., 1934). When the reference is to a periodical of which two volumes are published during a year the number put first indicates the first or second volume of the year followed by the year, and the last number refers to the page, thus, *Brit. med. J.*, i/1932, 250. When only one volume of a periodical is published each year, the reference gives the year and the page, thus, *Quart. J. Pharm.*, 1934, 341. In other cases the volume number is given in italics in addition to the year and page, thus, *J. biol. Chem.*, 1928, 77, 797.

α .—optical rotation.

A.O.A.C.—Association of Official Agricultural Chemists.

A.R.—List of Reagents for Analytical Purposes prepared by a special Committee appointed by the Councils of the Institute of Chemistry of Great Britain and Ireland and the Society of Public Analysts and other Analytical Chemists.—London, 1915.

Acta paediatr., Stockh.—Acta paediatrica.

Allen.—Allen's Commercial Organic Analysis. 5th Edn., Vols. I-VI edited by S. S. Sadtler, E. C. Lathrop and C. A. Mitchell; Vols. VII-X edited by C. A. Mitchell (1924-1933). Vol. IX, 4th Edn., 1917, edited by W. A. Davis.

Amer. J. Hyg.—American Journal of Hygiene.

Amer. J. Pharm.—American Journal of Pharmacy.

Amer. J. Physiol.—American Journal of Physiology.

Amer. J. publ. Hlth—American Journal of Public Health.

Amer. J. Syph.—American Journal of Syphilis.

Amer. J. trop. Med.—American Journal of Tropical Medicine.

Amer. perfum.—American Perfumer and Essential Oil Review.

Amer. Rev. Tuberc. (Suppl.)—American Review of Tuberculosis (Supplement).
Analyst.—Analyst.

Ann. Eugen., Camb.—Annals of Eugenics.

Ann. Falsif.—Annales des Falsifications.

Ann. Hyg. publ., Paris.—Annales d'hygiène publique et de médecine légale (industrielle et sociale).

Ann. Inst. Pasteur.—Annales de l'Institut Pasteur.

Ann. trop. Med. Parasit.—Annals of Tropical Medicine and Parasitology.

Apothekerztg, Berl.—Apothekerzeitung, Berlin.

Arch. Dis. Childh.—Archives of Disease in Childhood.

Arch. exp. Path. Pharmak.—Archiv für experimentelle Pathologie u. Pharmakologie.

Arch. intern. Med.—Archives of Internal Medicine.

Arch. Kinderheilk.—Archiv für Kinderheilkunde.

Arch. Méd. Enf.—Archives de médecine des enfants.

Arch. Pharm., Berl.—Archiv der Pharmazie.

Arch. Neurol. Psychiat., Lond.—Archives of Neurology and Psychiatry.

Arch. Radiol. Electrother.—Archives of Radiology and Electrotherapy.

b.p.—boiling-point.

B.P. '14.—British Pharmacopœia, 1914.

B.P. '32.—British Pharmacopœia, 1932.

B.P.C.—British Pharmaceutical Codex, 1934.

B.P.C. 1894 or 1901.—Formulary of the British Pharmaceutical Conference.

Barnett.—Preparation of Organic Compounds, by E. de Barry Barnett, 2nd Edn., 1920.

Batty Shaw.—Organotherapy, or Treatment of Disease by means of Preparation of Various Organs, by H. Batty Shaw.

Ber. dtsh. chem. Ges.—Bericht der Deutschen Chemischen Gesellschaft.

Berl. klin. Wschr.—Berliner klinische Wochenschrift.

Biochem. J.—Biochemical Journal.

Biochem. Z.—Biochemische Zeitschrift.

- Boll. Ist. sieroter.*, Milano—Bollettino del'Istituto sieroterapico milanese.
- Bower and Gwynne-Vaughan*.—Practical Botany for Beginners by F. O. Bower and Dame H. Gwynne-Vaughan, 1918.
- Brit. chem. Abstr.*—British Chemical Abstracts. (A) Pure Chemistry. (B) Applied Chemistry.
- Brit. colon. Drugg.*—British and Colonial Druggist (since 1915—British and Colonial Pharmacist).
- Brit. colon. Pharm.*—British and Colonial Pharmacist.
- Brit. J. Actino-Therap.*—British Journal of Actinotherapy and Physiotherapy.
- Brit. J. Biophys.*—British Journal of Biophysics.
- Brit. J. Child. Dis.*—British Journal of Children's Diseases.
- Brit. J. Derm.*—British Journal of Dermatology.
- Brit. J. exp. Path.*—British Journal of Experimental Pathology.
- Brit. J. phys. Med.*—British Journal of Physical Medicine.
- Brit. J. Radiol. (B.A.R.P. Sect.)*.—British Journal of Radiology (British Association for the Advancement of Radiology and Physiotherapy Section), continued since 1927 as British Journal of Radiology, New Series.
- Brit. J. Radiol. N.S.*—British Journal of Radiology, New Series.
- Brit. J. Radiol. (Röntg. Soc. Sect.)*.—British Journal of Radiology (Röntgen Society Section), continued since 1927 as British Journal of Radiology, New Series.
- Brit. J. Surg.*—British Journal of Surgery.
- Brit. med. J.*—British Medical Journal.
- Brit. med. J. Epit.*—British Medical Journal Epitome.
- Brompton H.*—Pharmacopœia of the Hospital for Consumption and Diseases of the Chest, 11th Edn., 1928.
- Brooke*.—Tropical Medicine, Hygiene and Parasitology, by Gilbert E. Brooke, 1920.
- Bruce and Dilling*.—Bruce and Dilling's Materia Medica and Therapeutics, by W. J. Dilling, 14th Edn., 1933.
- Bull. Dep. Agric. Can.*—Bulletin of the Department of Agriculture of the Dominion of Canada.
- Bull. imp. Inst., Lond.*—Bulletin of the Imperial Institute.
- Bull. Féd. int. Pharm.*—Bulletin de la Fédération internationale pharmaceutique.
- Bull. Inst. Pasteur*—Bulletin de l'Institut Pasteur.
- Bull. Off. int. Hyg. publ.*—Bulletin mensuel de l'Office internationale d'hygiène publique.
- Bull. Soc. chim. Fr.*—Bulletin, Société chimique de France.
- Bull. tech. Mus., Sydney*.—Bulletin of the Technological Museum, Sydney.
- Cc.*—cubic centimetre. See also Preface.
- C.H.W.*—Formulæ of Chelsea Hospital for Women, 1927.
- C.L.T.*—Formulæ of the Central London Throat, Nose and Ear Hospital, 3rd Edn., 1924.
- C.R.*—Changes proposed in the British Pharmacopœia by the International Agreement for the Unification of Pharmacopœial Formulæ for Potent Medicines, Brussels, Nov. 29, 1906, from a report to the Pharmacopœia Committee of the General Medical Council. Adopted March 4, 1907. This Committee issued further reports in 1908, 1910 and 1911. Cf. I.A.
- C.X.*—Charing Cross Hospital Pharmacopœia, 1922.
- Canad. Form.*—The Canadian Formulary, 1933.
- Canad. med. Ass. J.*—Canadian Medical Association Journal.
- Chem. Abstr.*—Chemical Abstracts.
- Chem. & Drugg.*—Chemist and Druggist.
- Chem. Ind. Rev.*—Chemistry and Industry Review.
- Chem. Z.*—Chemische Zeitschrift.
- Chininum*.—Chininum Scriptiones Collectae, Bureau for increasing the use of Quinine, Amsterdam, 1925.
- Clin. J.*—Clinical Journal.
- cm.*—centimetre.
- Colyer*.—Colyer's Dental Surgery and Pathology, by Sir J. F. Colyer, 6th Edn., 1931 and earlier issues (previously Smale and Colyer's Diseases and Injuries of Teeth).
- C.R. Acad. Sci., Paris*.—Compte rendu hebdomadaire des séances de l'Académie des sciences.
- C.R. Soc. Biol., Paris*.—Compte rendu hebdomadaire des séances et mémoires de la Société de biologie.

- Cushny*.—Text-book of Pharmacology and Therapeutics, by A. R. Cushny, 10th Edn., revised by C. W. Edmunds and J. A. Gunn (1934).
- D.D.A.*—Drugs or preparations coming within the scope of the Dangerous Drugs Acts, 1920 and 1923, and Consolidated Regulations, 1928.
- Dansk Tidsskr. Farm.*—Dansk Tidsskrift for Farmaci.
- Dtsch. med. Wschr.*—Deutsche medizinische Wochenschrift.
- Digitalis Assay*.—W. H. Martindale. A communication to the Pharmaceutical Society of Great Britain, 1913. (H. K. Lewis & Co., Ltd.)
- Disp.*—Art of Dispensing, published by *The Chemist and Druggist*, London, 10th Edn., 1926.
- Dixon*.—Manual of Pharmacology, by the late W. E. Dixon, F.R.S., 7th Edn., 1929.
- E.*—Pharmacopœia of the Evelina Hospital for Sick Children, Southwark, 1906.
- E.G.A.*—Pharmacopœia of the Elizabeth Garrett-Anderson Hospital, 1926.
- Ec. Prod. India*.—Economic Products of India.
- Edinb. med. J.*—Edinburgh Medical Journal.
- Emery*.—Clinical Bacteriology and Hæmatology, by W. d'Este Emery, 6th Ed., 1921.
- Evans*.—Evans' Analytical Notes (Evans Sons, Lescher & Webb Ltd., Liverpool).
- F.E.*—Farmacopea Espanola. Octava Edicion, 1930.
- F.N.*—Formulaire des Médicaments Nouveaux, by Dr. R. Weitz, 1933, Bockquillon-Limousin.
- f.p.*—freezing-point.
- Fr. Cx.*—Codex Medicamentarius Gallicus, Pharmacopée Française (1908).
- Fr. Cx. Supp. I to V.*—Supplements I (1920) to V (1926) of the Codex Medicamentarius Gallicus.
- Finnemore*.—Essential Oils, their Chemistry and Technology, by H. Finnemore, 1926.
- g.*—gramme.
- G.H.*—Pharmacopœia of Guy's Hospital, 1916.
- G.N.C.*—Pharmacopœia of the Gt. Northern Central Hospital, 1908 (see also *R.N.H.*).
- Garrod*.—Inborn Errors of Metabolism, 1923, and other communications by Sir A. E. Garrod.
- Garrod and Tirard*.—The Essentials of Materia Medica and Therapeutics, by Sir A. E. Garrod and Sir N. J. C. Tirard, 13th Edn., 1890.
- Gehe*.—Gehe's Codex, 6th Edn., 1933.
- Ghosh*.—Treatise on Materia Medica and Therapeutics, by the late R. Ghosh I.M.S. Edited by B. H. Deane, 12th Edn., 1930.
- Glasg. med. J.*—Glasgow Medical Journal.
- Gm.*—gramme (in doses). (See also Preface.)
- gr.*—grain.
- Gradwohl and Blaivas*.—The Newer Methods of Blood and Urine Chemistry by R. B. H. Gradwohl and A. J. Blaivas, 2nd Edn., 1920.
- Gr. Orm. H.*—Pharmacopœia of the Hospital for Sick Children, Great Ormond Street, 1931.
- Green*.—Green's Encyclopedia of Medicine and Surgery, 11 vols., 1906-11.
- Hager*.—Handbuch der Pharmaceutischen Praxis, revised by G. Fredericks G. Arends and H. Zörnig, 1925.
- Hale-White*.—Hale-White's Materia Medica, Pharmacy, Pharmacology and Therapeutics, revised by A. H. Douthwaite, 21st Edn., 1932.
- Hare*.—Text-Book of Practical Therapeutics, by H. A. Hare, 21st Edn., 1930.
- Harper Adams Util. Poult. J.*—Harper Adams Utility Poultry Journal.
- Helv. chim. Acta*.—Helvetica chimica acta.
- Hewlett*.—Serum and Vaccine Therapy, by T. R. Hewlett, 2nd Edn., 1910, also Bacteriology, 8th Edn., 1926.
- Hewlett and McIntosh*.—A Manual of Bacteriology, 9th Edn., revised by R. T. Hewlett and J. McIntosh, 1932.
- Hoppe-Seyl. Z.*—Hoppe-Seyler's Zeitschrift für physiologische Chemie.
- Hospitalstidende*.—Hospitalstidende.
- Hutchinson*.—Food and Principles of Dietetics, by R. Hutchinson, 6th Edn., 1926.
- I.A.*—International Agreement, 1930.
- I.D.C.*—Indigenous Drugs Committee, 2nd Report, Simla, 1909; 3rd Report Calcutta, 1916.
- I.V.*—iodine value.
- I. c. Add.*—Indian and Colonial Addendum (1900) to the B.P. 1898.

- Indian J. med Res.*—Indian Journal of Medical Research.
Indian med. Gaz.—Indian Medical Gazette.
Indian med. Res. Mem.—Indian Medical Research Memoirs.
Industr. Engng Chem. (anal. Edn.)—Industrial and Engineering Chemistry, (Analytical Edition).
Int. Conf. trop. Am.—Proceedings of the International Conference on Health Problems in Tropical America, 1924, United Fruit Co., Boston.
Int. Cong.—VIIth International Congress of Applied Chemistry, London, 1909; also VIIIth Congress, Washington, 1912.
J. R. Army med. Cps—Journal of the Royal Army Medical Corps.
J. R. nav. med. Serv.—Journal of the Royal Naval Medical Service.
J. agric. Sci.—Journal of Agricultural Science.
J. Amer. chem. Soc.—Journal of the American Chemical Society.
J. Amer. diet. Ass.—Journal of the American Dietetic Association.
J. Amer. med. Ass.—Journal of the American Medical Association.
J. Amer. pharm. Ass.—Journal of the American Pharmaceutical Association.
J. Ass. off. agric. Chem., Wash.—Journal of the Association of Official Agricultural Chemists.
J. biol. Chem.—Journal of Biological Chemistry.
J. Cancer Res.—Journal of Cancer Research.
J. chem. Soc.—Journal of the Chemical Society.
J. chem. Soc. Abstr.—Journal of the Chemical Society Abstracts (continued since 1926 as British Chemical Abstracts).
J. clin. Invest.—Journal of Clinical Investigation.
J. clin. Res.—Journal of Clinical Research.
J. comp. Path.—Journal of Comparative Pathology and Therapeutics.
J. exp. Med.—Journal of Experimental Medicine.
J. Hyg., Camb.—Journal of Hygiene.
J. Immunol.—Journal of Immunology.
J. infect. Dis.—Journal of Infectious Diseases.
J. Lab. clin. Med.—Journal of Laboratory and Clinical Medicine.
J. ment. Sci.—Journal of Mental Science.
J. Path. Bact.—Journal of Pathology and Bacteriology.
J. Pharm. Chim., Paris.—Journal de pharmacie et de chimie.
J. Pharmacol.—Journal of Pharmacology and Experimental Therapeutics.
J. Physiol.—Journal of Physiology.
J. Röntgen Soc.—Journal of the Röntgen Society, continued from 1924 to 1927 as The British Journal of Radiology (Röntgen Society Section), and since 1927 as The British Journal of Radiology, New Series.
J. State Med.—Journal of State Medicine.
J. Soc. chem. Ind., Lond.—Journal of the Society of Chemical Industry.
J. Suisse Pharm.—Journal suisse de pharmacie, now Schweizerische Apothekerzeitung.
J. Text. Inst., Manchr—Journal of the Textile Institute, Manchester.
J. trop. Med. (Hyg.)—Journal of Tropical Medicine and Hygiene.
K.C.H.—King's College Hospital Pharmacopœia, 1934.
Kenwood—Public Health Laboratory Work, by H. R. Kenwood, 8th Edn., 1925.
Klin. Wschr.—Klinische Wochenschrift.
Knox—Radiography and Radio-Therapeutics, by Robert Knox, 4th Edn., in 2 vols. (Vol. II completed and edited by W. M. Levitt, 1923-32).
L.H.—The London Hospital Pharmacopœia, 1934.
L.L.—The London Lock Hospitals Pharmacopœia.
Lancet—Lancet.
Leprosy Rev.—Leprosy Review.
m.—minim.
m.a.—milliampere.
m.p.—melting-point.
M.R.C.—Medical Research Council.
Mann.—Physiology and Pathology of the Urine, by J. Dixon Mann, 2nd Edn., 1908.
May.—Chemistry of Synthetic Drugs, by Percy May, 3rd Edn., 1921.
Med. Annu.—Medical Annual.
Med. J. Rec.—Medical Journal and Record.
Med. Offr—Medical Officer.
Med. Pr.—The Medical Press and Circular.
Medicine, Baltimore.—Medicine, Baltimore.
Mem. Univ. Calif.—Memoirs of the University of California.

- Merck's A. R.*—E. Merck's Annual Report of recent advances in Pharmaceutical Chemistry and Therapeutics.
- Merck's Index.*—Merck's Index, 5th Edn., 1927.
- Mfg Chem.*—The Manufacturing Chemist.
- mg.*—milligramme.
- ml.*—millilitre.
- Mod. Tech. in Treatment.*—Modern Technique in Treatment, Vols. 1-4, 1925-28, *The Lancet*, London.
- Morgan.*—Organic Compounds of Arsenic and Antimony, by G. T. Morgan, 1918.
- Muir and Ritchie.*—Manual of Bacteriology, by R. Muir and J. Ritchie, 9th Edn., 1932.
- Münch. med. Wschr.*—Münchener medizinische Wochenschrift.
- Murrell.*—What to do in Cases of Poisoning, by William Murrell, 13th Edn., 1925, revised by P. Hamill.
- Mx. H.*—Middlesex Hospital Pharmacopœia, 1927.
- Myers.*—Practical Chemical Analysis of Blood, by V. C. Myers, 2nd Edn., 1924.
- n*—refractive index.
- Nature, Lond.*—Nature, London.
- Naturwissenschaften*—Naturwissenschaften.
- N.F. V*—National Formulary of Unofficial Preparations, issued by the American Pharmaceutical Association, 5th Edn., 1926.
- N.H.W.*—Pharmacopœia of the New Hospital for Women, London, 1904. (For some formulæ not included in E.G.A.)
- N.I.F.*—National Formulary for National Health Insurance Purposes, issued by the British Medical Association, 2nd Edn., 1933.
- N.N.R.*—New and Non-official Remedies, issued by the American Medical Association.
- N.S.D.*—National Standard Dispensatory, in accordance with *U.S.P. VIII*, 1905.
- New Engl. J. Med.*—New England Journal of Medicine.
- Newth.*—Text-Book of Inorganic Chemistry, by G. S. Newth, 1923.
- Nutr. Abstr. Rev.*—Nutrition Abstracts and Reviews.
- N.Y. St. J. Med.*—New York State Journal of Medicine.
- P**1.—Part I, Poisons Schedule, 1908.
- P**—Part II, Poisons Schedule, 1908.
- P.E.H.C.*—Pharmacopœia of the Princess Elizabeth of York Hospital for Children, 1933 (formerly the East London Hospital).
- P.G. VI.*—German Pharmacopœia, 1926.
- P.J.F.*—Pharmaceutical Journal Formulary.
- P.L.*—Pharmacopœia Londinensis, 1851.
- P.M.C.E.*—Select Parliamentary Committee on Proprietary Medicines Enquiry 1912-13.
- P.N.F.*—Proposed National Formulary (U.S.).
- P. Argent II.*—Pharmacopœia of the Argentine Republic, 2nd. Edn., 1919.
- Paris méd.*—Paris médical. La semaine du clinicien.
- P. Austr.*—Austrian Pharmacopœia, 1906.
- P. Belg. IV.*—Belgian Pharmacopœia, 1930.
- P. Dan.*—Danish Pharmacopœia, 1933.
- P. Helv. V.*—Swiss Pharmacopœia. 1933.
- P. Ind.*—Pharmacopœia of India, 1868.
- P. Ital.*—Italian Pharmacopœia, 1929.
- P. Jap.*—Japanese Pharmacopœia, 1921 (English translation, 1922).
- P. Mex.*—Mexican Pharmacopœia, 1926.
- P. Ned.*—Netherlands Pharmacopœia, 1926.
- P. Off.*—Proposed official recommendations as embodied in reports of Pharmacopœia Commission Sub-Committees, issued by the General Medical Council, 1930, onwards.
- P. Russ.*—Russian Pharmacopœia, 1926.
- P. Svec.*—Swedish Pharmacopœia, 1925.
- Perfum. essent. Oil Rec.*—Perfumery and Essential Oil Record.
- Ph.*—Pharmacopœia, by E. White and J. Humphrey, 1909.
- Ph. Form.*—Pharmaceutical Formulas, 9th Edn., Second Reprint, 1921, by Peter MacEwan; and 10th Edn., Vol. I, 1929, revised by S. W. Woolley and G. P. Forrester, Vol. II, 1934, revised by G. P. Forrester, *The Chemist and Druggist* London.
- Ph. Notes.*—Pharmacy Notes from various parts of the World, by W. H. Martindale, 1907.

- Pharm. J.*—Pharmaceutical Journal.
Pharm. Weekbl.—Pharmaceutisch Weekblad voor Nederland.
Pharm. Ztg, Berl.—Pharmazeutische Zeitung.
Pharmacol.—Chemical Basis of Pharmacology, by Francis Francis and J. M. Fortescue-Brickdale, 1908.
Philipp. J. Sci.—Philippine Journal of Science.
Physiol. Rev.—Physiological Reviews.
Plaistow.—Pharmacopœia of St. Mary's Hospital for Women and Children, Plaistow, 1913.
Pr. méd.—Presse médicale.
Practitioner.—Practitioner.
Prescriber.—Prescriber.
Proc. chem. Soc., Lond.—Proceedings of the Chemical Society, London.
Proc. Mayo Clin.—Proceedings of Staff Meetings of the Mayo Clinic.
Proc. roy. Soc.—Proceedings of the Royal Society.
Proc. roy. Soc. Edinb.—Proceedings of the Royal Society of Edinburgh.
Proc. R. Soc. Med.—Proceedings of the Royal Society of Medicine.
Proc. Soc. exp. Biol., N.Y.—Proceedings of the Society for Experimental Biology and Medicine.
Prov. Hosp.—Provincial Hospital Pharmacopœias, issued by *The Chemist and Druggist*, London, 1913.
Publ. Hlth, Lond.—Public Health.
Publ. Hlth Rep., Wash.—Public Health Reports, issued by the United States Public Health Service.
Q.H.C.—Pharmacopœia of the Queen's Hospital for Children (formerly the North-Eastern Hospital), 1927.
Quart. Bull. Hlth Org. L. o. N.—Quarterly Bulletin of the Health Organisation of the League of Nations.
Quart. J. exp. Physiol.—Quarterly Journal of Experimental Physiology.
Quart. J. Med.—Quarterly Journal of Medicine.
Quart. J. Pharm.—Quarterly Journal of Pharmacy and Pharmacology.
R.D.H.—Pharmacopœia of the Royal Dental Hospital, London, 1926.
R.F.H.—Pharmacopœia of the Royal Free Hospital, London, 1922.
R.N.H.—Pharmacopœia of the Royal Northern Group of Hospitals, 1930.
R.O.H.—Pharmacopœia of the Royal Ophthalmic Hospital, 1929.
R.V.I.—Pharmacopœia of the Royal Victoria Infirmary, Newcastle-on-Tyne.
Rem.—Remington's Practice of Pharmacy, 7th Edn., 1926.
Rep. Brit. Emp. Cancer Campgn—Report of the British Empire Cancer Campaign.
Rep. Cancer Res. Fd—Report of the Imperial Cancer Research Fund.
Rep. Inst. med. Res. F.M.S.—Report of the Institute for Medical Research, Federated Malay States.
Rep. med. Offr Minist. Hlth, Lond.—Report of the Chief Medical Officer, the Ministry of Health.
Rep. med. Res. Coun., Lond.—Report of the Medical Research Council.
Rep. metrop. Asylums Bd—Report of the Metropolitan Asylums Board.
Rep. metrop. Wat. Bd—Report of the Metropolitan Water Board.
Rep. publ. Hlth med. Subj., Lond.—Report on Public Health and Medical Subjects, Ministry of Health.
Retail Chem.—Retail Chemist.
Ringer and Sainsbury.—Handbook of Therapeutics, by Sidney Ringer and Harrington Sainsbury, 13th Edn., 1897.
Rutherford.—Radioactive Substances and their Radiations, by E. Rutherford, 1912.
S.H.—Pharmacopœia of the Samaritan Free Hospital, 1926.
S.H.D.—Steeven's Hospital (Dublin) Formulary, 3rd Edn., 1930.
S.R.A., F.D., No. 2, Rev. 4.—Service and Regulatory Announcements, Food and Drug No. 2 (Fourth Revision); issued by the United States Department of Agriculture, Food and Drug Administration, August 1933.
S.R. & O.—Statutory Rules and Orders, His Majesty's Stationery Office, London.
S.V.—saponification value.
St. Bart's H.—Pharmacopœia of St. Bartholomew's Hospital, 1921.
St. G.H.—Pharmacopœia of St. George's Hospital, 1927.
St. J.H.—Pharmacopœia of St. John's Hospital for Skin Diseases, 1926.
St. M.H.—Pharmacopœia of St. Mary's Hospital, 1934.
St. T.H.—Pharmacopœia of St. Thomas' Hospital, 1931.
S. Afr. med. J.—South African Medical Journal.

- Salvarsan*.—Salvarsan: Its Chemistry, Pharmacy and Therapeutics, by Martindale and Westcott, 1911.
- Schmidt*.—Ausführliches Lehrbuch der Pharmaceutischen Chemie, Vol. I (Inorganic), Vol. II (Organic), Part I (1922), Part II (1923), by Ernst Schmidt.
- Schweiz. ApothZtg*.—Schweizerische Apothekerzeitung.
- Sci. Rep. Cancer Res. Fd, Lond.*.—Scientific Reports on the Investigations of the Imperial Cancer Research Fund.
- Secret Remedies*.—Secret Remedies, What they Cost and What they Contain.—British Medical Association (1909); also "More Secret Remedies" (1912).
- Seidell*.—Solubilities of Inorganic and Organic Substances, 2nd Edn., 1920.
- Soddy*.—Interpretation of Radium, by F. Soddy, 4th Edn., 1920.
- Sp. gr.*.—specific gravity.
- Spec. Rep. Food Invest. Bd, Lond.*.—Special Report, Food Investigation Board, Department of Scientific and Industrial Research.
- Spec. Rep. Ser. med. Res. Comm.*.—National Health Insurance, Medical Research Committee, Special Report Series.
- Spec. Rep. Ser. med. Res. Coun., Lond.*.—Special Report Series, Medical Research Council, London.
- Stitt*.—Practical Bacteriology, Blood Work and Animal Parasitology, by E. R. Stitt, 8th Edn., 1927.
- Svensk farm. Tidskr.*.—Svensk farmaceutisk Tidskrift.
- System of Dietetics*.—By various authors, edited by G. A. Sutherland, 1908.
- T.H.*.—Pharmacopœia of the Golden Square Throat, Nose and Ear Hospital, 1935.
- T.M.*.—Trade Mark (British), with Registered No. in brackets.
- Teetgen*.—Profitable Herb Growing and Collecting, by Ada B. Teetgen, 1916.
- Thorpe*.—Dictionary of Applied Chemistry, 7 vols., edited by Sir E. Thorpe (Vols. VI and VII with assistance of H. F. Morley), 1921-1927; and Supplement, Vol. I, by J. F. Thorpe and M. A. Whiteley, 1934.
- Tibbles*.—Theory of Ions, a Consideration of its Place in Biology and Therapeutics, by William Tibbles, 1908.
- Tilley*.—Diseases of the Nose and Throat, by Herbert Tilley, 4th Edn., 1919.
- Topley and Wilson*.—The Principles of Bacteriology and Immunity, by W. W. C. Topley and G. S. Wilson, 1929.
- Trans. R. Soc. trop. Med. Hyg.*.—Transactions of the Royal Society of Tropical Medicine and Hygiene.
- Trop. Dis. Bull.*.—Tropical Diseases Bulletin.
- U.C.H.*.—Pharmacopœia of University College Hospital, 1933.
- U.F.C. '25*.—Fourteenth Annual Report, United Fruit Co., Medical Dept., 1925.
- U.S.D.*.—United States Dispensatory, 21st Edn., 1926.
- U.S.P. X*.—Pharmacopœia of the United States, 1925.
- V.H.C.*.—Pharmacopœia of the Victoria Hospital for Children (Chelsea), 1920.
- v/v*.—volume in volume.
- v/w*.—volume in weight.
- Vet. J.*.—Veterinary Journal.
- Vic. Park*.—City of London Hospital for Diseases of the Heart and Lungs, Victoria Park, E.2, 1926.
- W.*.—Pharmacopœia of the Hospital for Women (Soho Square), 1927.
- w/v*.—weight in volume.
- w/w*.—weight in weight.
- W.H.*.—Pharmacopœia of Westminster Hospital, 1934.
- W.W.W.*.—W. Wynn Westcott, collaborator with the late Dr. W. H. Martindale in the preparation of the Extra Pharmacopœia, 1883-1925.
- Ward and Smith*.—Recent Advances in Radium, by W. Roy Ward and A. J. Durden Smith, 1933.
- Watts*.—Dictionary of Chemistry, by M. M. Pattison Muir and H. Forster Morley, 4 vols., 1889-1894; reprinted 1918-1920.
- Wenyon*.—Protozoology, by C. M. Wenyon, 2 vols., 1926.
- Wynter Blyth*.—Foods: Their Composition and Analysis, by the late A. Wynter Blyth and M. Wynter Blyth, 7th Edn., revised by H. E. Cox, 1927.
- Yearb. Pharm.*.—The Yearbook of Pharmacy (since 1928 The Quarterly Journal of Pharmacy and Pharmacology).
- Yeo*.—Manual of Medical Treatment, by I. Burney Yeo, 5th Edn., 1913.
- Z. anal. Chem.*.—Zeitschrift für analytische Chemie.
- Z. ImmunForsch.*.—Zeitschrift für Immunitätsforschung und experimentelle Therapie.
- Z. Hyg. InfektKr.*.—Zeitschrift für Hygiene und Infektionskrankheiten.

APPROXIMATE EQUIVALENTS

WEIGHTS. IMPERIAL TO METRIC.

grain	gramme	grain	gramme	grains	grammes
$\frac{1}{1000}$ =	0.000065	$\frac{1}{4}$ =	0.016	15 =	1.0
$\frac{1}{200}$ =	0.0003	$\frac{1}{3}$ =	0.02	20 =	1.2
$\frac{1}{100}$ =	0.0006	$\frac{1}{2}$ =	0.03	30 =	2.0
$\frac{1}{64}$ =	0.001	$\frac{3}{4}$ =	0.05	45 =	3.0
$\frac{1}{50}$ =	0.0013	1 =	0.06	60 =	4.0
$\frac{1}{40}$ =	0.0015	grains	gramme	90 =	6.0
$\frac{1}{32}$ =	0.002	$1\frac{1}{2}$ =	0.1	120 =	8.0
$\frac{1}{25}$ =	0.0025	2 =	0.12	150 =	10.0
$\frac{1}{20}$ =	0.003	3 =	0.2	180 =	12.0
$\frac{1}{16}$ =	0.004	4 =	0.25	$\frac{1}{2}$ ounce	
$\frac{1}{12}$ =	0.005	5 =	0.3	(av.) =	15.0
$\frac{1}{10}$ =	0.006	6 =	0.4	1 „ =	30.0
$\frac{1}{8}$ =	0.008	8 =	0.5	(or nearer	28.35)
$\frac{1}{6}$ =	0.01	10 =	0.6	1 pound	
$\frac{1}{5}$ =	0.012	12 =	0.8		=453.59

WEIGHTS. METRIC TO IMPERIAL.

1 kilogramme	=	2 lb.	$3\frac{1}{4}$ oz.
500 grammes	=	1 „	$1\frac{5}{8}$ „
100 „	=	$3\frac{1}{2}$ oz.	
25 „	=	$\frac{7}{8}$ „	
10 „	=	$\frac{1}{3}$ „	
1 „	=	15.43 grains	
$\frac{1}{2}$ „	or 500 milligrammes	=	7.7 „	

MEASURES. IMPERIAL TO METRIC.

minim	ml.	minims	ml.	fluid oz.	ml.
$\frac{1}{2}$ =	0.03	15 =	1.0	1 =	30.0
1 =	0.06	20 =	1.2	fluid ozs.	
minims		25 =	1.5	2 =	60.0
2 =	0.12	30 =	2.0	4 =	115.0
3 =	0.2	40 =	2.5	5 =	140.0
4 =	0.25	45 =	3.0	5 =	170.0
5 =	0.30	60 =	4.0	8 =	230.0
6 =	0.4	90 =	6.0	10 =	280.0
8 =	0.5	120 =	8.0	20 =	568.0
10 =	0.6	240 =	15.0	gallon	litres
12 =	0.8			1 =	4.536

MEASURES. METRIC TO IMPERIAL.

1 ml.	=	15 (nearer 17) minims.
1 litre	=	1 pint 15 fl. oz. approx.

MEASURES OF LENGTH.

1 micromillimetre	=	$\frac{1}{1000000}$ millimetre, usually represented by $m\mu$.
1 micron	=	$\frac{1}{1000}$ millimetre, or 1 micrometre „ „ μ .
1 millimetre	=	0.03937 inch.
1 centimetre	=	0.3937 inch.
1 decimetre	=	3.937 inches.
1 metre	=	39.370113 inches or 1 yard 3.37 inches nearly.

INTERNATIONAL (1935) ATOMIC WEIGHTS

Element.	Sym- bol.	Atomic Weight.	Element.	Sym- bol.	Atomic Weight.
Aluminium ..	Al	26·97	Molybdenum ..	Mo	96·0
Antimony ..	Sb	121·76	Neodymium ..	Nd	144·27
Argon ..	A	39·944	Neon ..	Ne	20·183
Arsenic ..	As	74·91	Nickel ..	Ni	58·69
Barium ..	Ba	137·36	Nitrogen ..	N	14·008
Beryllium ..	Be	9·02	Osmium ..	Os	191·5
Bismuth ..	Bi	209·00	Oxygen ..	O	16·0000
Boron ..	B	10·82	Palladium ..	Pd	106·7
Bromine ..	Br	79·916	Phosphorus ..	P	31·02
Cadmium ..	Cd	112·41	Platinum ..	Pt	195·23
Calcium ..	Ca	40·08	Potassium ..	K	39·096
Carbon ..	C	12·00	Praseodymium	Pr	140·92
Cerium ..	Ce	140·13	Radium ..	Ra	225·97
Cesium ..	Cs	132·91	Radon ..	Rn	222·00
Chlorine ..	Cl	35·457	Rhenium ..	Re	186·31
Chromium ..	Cr	52·01	Rhodium ..	Rh	102·91
Cobalt ..	Co	58·94	Rubidium ..	Rb	85·44
Columbium ..	Cb	92·91	Ruthenium ..	Ru	101·7
Copper ..	Cu	63·57	Samarium ..	Sm	150·43
Dysprosium ..	Dy	162·46	Scandium ..	Sc	45·10
Erbium ..	Er	167·64	Selenium ..	Se	78·96
Europium ..	Eu	152·0	Silicon ..	Si	28·06
Fluorine ..	F	19·00	Silver ..	Ag	107·880
Gadolinium ..	Gd	157·3	Sodium ..	Na	22·997
Gallium ..	Ga	69·72	Strontium ..	Sr	87·63
Germanium ..	Ge	72·60	Sulphur ..	S	32·06
Gold ..	Au	197·2	Tantalum ..	Ta	181·4
Hafnium ..	Hf	178·6	Tellurium ..	Te	127·61
Helium ..	He	4·002	Terbium ..	Tb	159·2
Holmium ..	Ho	163·5	Thallium ..	Tl	204·39
Hydrogen ..	H	1·0078	Thorium ..	Th	232·12
Indium ..	In	114·76	Thulium ..	Tm	169·4
Iodine ..	I	126·92	Tin ..	Sn	118·70
Iridium ..	Ir	193·1	Titanium ..	Ti	47·90
Iron ..	Fe	55·84	Tungsten ..	W	184·0
Krypton ..	Kr	83·7	Uranium ..	U	238·14
Lanthanum ..	La	138·92	Vanadium ..	V	50·95
Lead ..	Pb	207·22	Xenon ..	Xe	131·3
Lithium ..	Li	6·940	Ytterbium ..	Yb	173·04
Lutecium ..	Lu	175·0	Yttrium ..	Y	88·92
Magnesium ..	Mg	24·32	Zinc ..	Zn	65·38
Manganese ..	Mn	54·93	Zirconium ..	Zr	91·22
Mercury ..	Hg	200·61			

ANALYTICAL ADDENDA TO CHEMICALS AND MATERIA MEDICA IN VOLUME I.

ACACIA

Acacia (*B.P.* '32). Occurs in rounded or ovoid tears and the powder does not comply with the official description. Loses not more than 15% of its weight at 100° and should yield not more than 5% of ash. (All *B.P.* ash values are calculated with reference to the drug dried at 100°). It should be free from tannins, starch and dextrans and the *B.P.* requires it to be almost entirely soluble in an equal volume of water, but the *U.S.P. X* permits not more than 1% of water-insoluble residue.

The best varieties are Kordofan, Mogadore and Senegal gums, but dark-coloured gums are not suitable for medicinal purposes.

The function of gum in official acacias is no doubt to preserve the moisture necessary to keep the plants alive during the months of drought—December to April. The cicatrization of the wounds, in collecting, is of secondary importance, the gum being exuded only during periods of extreme dryness, the process stopping with the slightest rain.—*E. Perrot, Pharm. J.*, ii/1920, 510.

Acidity of Gum Acacia. The amount of sodium hydroxide required to neutralise 1000 g. of gum varies from 2.48 to 3.2 g., giving an average of 2.84 g. The clarity of the solution is in no way related to its reaction.

A sample of mucilage two months old showed that in a sterile solution preserved with benzoic acid relatively no hydrolysis of the component salts had occurred.

The identification of common gums. Acacia, tragacanth, agar, Irish moss, quince, and ghatti gum distinguished by Millon's lead acetate, potassium hydroxide, tannic acid, etc. A useful table.—*Pharm. J.*, ii/1931, 46.

ACIDUM ACETICUM

Acidum Aceticum (*B.P.* '32). Contains from 32.5% to 33.5% *w/w* of $\text{CH}_3\cdot\text{COOH}$; sp. gr., 1.044 to 1.045. The diluted acid, Acidum Aceticum Dilutum, now contains 6% *w/w*, whereas the corresponding acid of the *B.P.* '14 contained only 5%. Acidum Aceticum Glaciale (*B.P.* '32) contains not less than 99% by weight with a f.p. of not less than 14.8° and a sp. gr. of 1.055 to 1.058.

The glacial and dilute acetic acids of the *U.S.P. X* are of the same strength, but Acidum Aceticum (*U.S.P. X*) contains from 6% to 37% by weight of $\text{CH}_3\cdot\text{COOH}$. Acidum aceticum, *P.G. VI*, contains not less than 96% and Acidum aceticum dilutum, *P.G. VI*, from 29.7% to 30.6% of $\text{CH}_3\cdot\text{COOH}$. Acidum aceticum concentratum and Acidum aceticum dilutum, *P. Helv. V*, contain 80% to 100% and 29.5% to 30.5% *w/w* respectively of $\text{CH}_3\cdot\text{COOH}$.

A British Standard Specification (*B.S.S.* No. 576—1934) has been issued by the British Standards Institution for Glacial Acetic Acid and Dilute Acetic Acids. The specification for Glacial Acetic Acid, 99% to 100%, includes description, acetic acid content, crystallising-point (not lower than 14.8°), residue on evaporation, iron, chlorides, sulphates, heavy metals, substances reducing permanganate, formic acid, aldehydes and ketonic substances, and sampling, and the appendices describe the methods and apparatus to be used. The specification for Dilute Acetic Acids deals with Acetic Acids, 80%, 60%, and 40%.

The iron which may be present in these substances is determined colorimetrically by means of thioglycollic acid in the presence of ammonia. *B.S.S.* No. 578—1934 refers to Technical Acetic Acid, 98% to 100%, and to Technical Acid 80%, 60%, and 40%.

Potassii Acetas (*B.P.* '32). $\text{CH}_3\cdot\text{COOK}=98\cdot12$. Loses not more than 5% of its weight at 100° and the dried salt contains not less than 99% of $\text{CH}_3\cdot\text{COO}$ when assayed by ignition and subsequent titration of the alkaline residue with acid. The *U.S.P. X* salt is of the same strength but should be dried at 150° .

Sodii Acetas (*B.P.C.* '34). $\text{CH}_3\cdot\text{COONa}\cdot3\text{H}_2\text{O}=136\cdot1$. The crystalline salt should contain the equivalent of 99.5% to 105% of the pure salt. Sodii Acetas *U.S.P. X*, contains from 59.97% to 62.96% of $\text{NaC}_2\text{H}_3\text{O}_2$, corresponding to not less than 99.5% of the crystalline salt.

Thallii Acetas (*B.P.C.* '34). $\text{CH}_3\cdot\text{COOTl}=263\cdot4$. Assayed gravimetrically by precipitating the base as thallos iodide, and contains not less than 98%.

Thallium Acetate Poisoning. Detailed account of disaster resulting in the death of 14 out of 16 schoolchildren under treatment for ringworm in an orphanage in Granada.—*Brit. med. J.*, i/1934, 25.

Zinci Acetas (*B.P.C.* '34). $(\text{CH}_3\cdot\text{COO})_2\text{Zn}\cdot2\text{H}_2\text{O}=219\cdot5$. Contains not less than 99.5% of the pure acetate when assayed on its zinc content by precipitation with mercuric ammonium thiocyanate solution and subsequent titration with iodate solution, as described in the Pharmacopœia for Zinci Sulphas. Zinc Acetas, *U.S.P. X*, contains from 83.16% to 87.32% of $\text{Zn}(\text{C}_2\text{H}_3\text{O}_2)_2$, corresponding to not less than 99.5% of the crystalline salt; it is assayed by precipitation as sulphide and weighing as oxide.

Acidum Trichloroaceticum (*B.P.* '32). $\text{CCl}_3\cdot\text{COOH}=163\cdot4$. Assayed by ignition with sodium carbonate and titration of the chloride formed with silver nitrate and ammonium thiocyanate and contains not less than 98% of the pure acid. The *U.S.P. X* acid, dried to constant weight over sulphuric acid, contains not less than 99% and is assayed by titration with normal sodium hydroxide solution.

Acetonum (*B.P.* '32). Sp. gr. at $15\cdot5^\circ$, 0.796 to 0.801. At least 95% by volume distils between 56° and 58° when measured under standard conditions. Tests for alkalinity, acidity, oxidisable substances, moisture, and residue on evaporation are also prescribed. The *U.S.P. X* prescribes an iodometric method for the assay of acetone and requires it to contain not less than 99% by weight of $\text{CH}_3\cdot\text{CO}\cdot\text{CH}_3$.

For most purposes commercially standardised acetone is good enough. It is not used for making any official galenicals.—*Pharm. J.*, ii/1932, 47.

Diacetone Alcohol. A British Standard Specification for Diacetone Alcohol 4-hydroxy-4-methyl-pentanone-2 (*B.S.S.* No. 549—1934), includes requirements regarding description, specific gravity, distillation range, flash-point, miscibility with water, water, acidity, and sampling.

Amyl Acetate. A British Standard Specification (*B.S.S.* No. 552—1934) for Amyl Acetate includes requirements regarding description, specific gravity, distillation range, residue on evaporation, water, acidity, ester content, and sampling.

Ethyl Acetate. A specification for Ethyl Acetate (*B.S.S.* No. 553—1934) includes requirements regarding description, specific gravity, distillation range, residue on evaporation, water, acidity, ester content (not less than 96%), and sampling.

Normal Butyl Acetate. *B.S.S.* No. 551—1934 for Normal Butyl Acetate (acetic ester of primary normal butyl alcohol) includes requirements regarding description, specific gravity, distillation range, residue on evaporation, acidity, ester content, and sampling. The appendices describe the methods and apparatus to be used.

ACIDUM ACETYLSALICYLICUM

Acidum Acetylsalicylicum (*B.P.* '32). Assayed by hydrolysis with excess of $\text{N}/2$ sodium hydroxide and titration with acid with a blank experiment under the same conditions. It contains not less than 99.5% of the pure compound, has a m.p. of 135° to 138° and a limit test for free salicylic acid by which the proportion does not exceed about 0.05%.

The m.p. of the *U.S.P. X* product is not below 132° and the test for free salicylic acid is equivalent to about 0.1%. Acidum acetylosalicylicum, *P. Helv. V*, is determined by titrating a solution in alcohol to phenolphthalein with N/10 sodium hydroxide and contains from 99.5% to 100% of the pure substance.

An official quantitative method for the determination of acetylsalicylic acid tablets is described in Methods of Analysis (A.O.A.C., 1930, 445).

Determination of Free Salicylic Acid in Acetylsalicylic Acid. Dissolve salicylic acid, 1 g., in alcohol, 60 ml., and adjust to 100 ml. with water. 10 ml. of this solution may then be diluted to 1000 ml. for the standard, making 1 ml. = 0.0001 g. acid. Dissolve 0.6 g. of the sample to be tested in 9 ml. of alcohol, dilute with water to 90 ml. and mix well. Take two exactly similar Nessler glasses. Into one pour 60 ml. of the solution, into the other the remaining 30 ml., together with 3 ml. of alcohol, and adjust to the volume of the first. This gives a difference of 0.2 g. of acetylsalicylic acid in similar mixtures of alcohol and water. One ml. of a 1% solution of iron alum is added to each, mixed, and the colour matched by adding the salicylic acid solution.—A. J. Jones, *Chem. & Drugg.*, 1919, 402.

A solution yields a buff-coloured precipitate with ferric chloride until hydrolysed by the addition of a little hydrochloric acid, which yields the typical violet colour of salicylate (developing particularly on warming).

The ferric chloride test for free salicylic acid in acetylsalicylic acid is insufficient to prevent adulteration, etc., in that the addition of borax, sodium phosphate, tartaric acid, citric acid and other oxy-acids will readily prevent or mask the colour ordinarily produced with ferric chloride.

Tartaric Acid added to aspirin tablets would mask the ferric iron test if salicylic acid were present. 1% of citric acid will mask the presence of 0.2% of free salicylic acid.—A. Nutter Smith, *Chem. & Drugg.*, ii/1930, 330.

Determination of Free Acetic Acid. A. Nutter Smith (*Yearb. Pharm.*, 1920, 21) described a process by which the sample (1 g.) previously finely powdered is spread on muslin and the acetic acid evolved is aspirated into 50 or 100 ml. of distilled water for $\frac{1}{2}$ or 1 hour. The liquid is then titrated with N/500 caustic soda. Each ml. of this represents 0.00012 g. of acetic acid.

Hydrolysis of Acetylsalicylic Acid and its Salts in Dilute Acid and in Water.

COMPOUND	SOLUTION	PERCENTAGE HYDROLYSIS						
		Immed. on dissolv- ing	After 1	2	3	4	5	24 hours.
Acetylsalicylic Acid	In water ..	Nil	0.5	1.3	2.0	2.9	4.0	20
	In 0.2% HCl.	Nil	1.3	2.4	3.9	4.7	7.6	38
Magnesium Acetylsalicylate (Magisal)	In water	2.2	3.3	5.5	7.8	9.1	12.5	33
	In 0.2% HCl.	2.2	3.3	5	5.5	7	8	28
Calcium Acetyl- salicylate (Tyl- calsin)	In water ..	1.6	3.2	6.3	9.5	10	14	38
	In 0.2% HCl.	1.6	3.2	4.6	5.4	7	8	35
Sodium Acetyl- salicylate (Tyl- natrin)	In water ..	1.5	2.9	6	7.3	8.8	11.7	30
	In 0.2% HCl.	1.5	2.9	4.4	5.3	6.5	7.3	30

The above table, according to experiments made in 1911 and 1925, shows the results for the hydrolysis of acetylsalicylic acid and its calcium, magnesium and sodium salts in water and in physiological acid (0.2% HCl) at 38° .

The solutions used were 1 in 500, and the amount of salicylic acid formed was determined by diluting 25 ml., or less, of the solution to 50 ml., adding 1 ml. of 1% ferric chloride solution and comparing in Nessler cylinders with the colour given by a standard sodium salicylate solution.

When the solution to be tested contained hydrochloric acid, an equivalent amount of N/4 caustic soda solution was added before the ferric chloride, to ensure that the colour should not be interfered with by the acid.

It is seen from these results that the amounts of acetylsalicylic acid and its salts hydrolysed after three hours' treatment with physiological acid are slight and show no great difference. Hence, the alkaline salts may be quite as useful in physiological action as the acid itself, and by reason of their greater solubility, in particular the calcium salt—should possess distinct advantage for promoting action.

The 24-hour results are given in the tables as matters of chemical interest rather than as being of physiological importance.

The conclusion is that in taking a dose of aspirin, or its salts, the amount absorbed while passing through the stomach does not exceed 5% of the amount taken.

It is suggested that aspirin ought to be fairly stable in the buffer mixture encountered in the alimentary canal, and in support of this it is stated that, after administration, quantities varying from 5.3% to 41% may be recovered from the urine.—*J. chem. Soc. Abstr.*, 1/1923, 870.

The decomposition of acetylsalicylic acid in aqueous solution in the presence of alkali citrate or acetate is independent of the concentration of the salt or of the acid. Solutions (at room temperature) decompose about 10% during the first day and 50% in a week. The rate of decomposition increases very rapidly with rise of temperature.—C. Morton, *Quart. J. Pharm.*, 1933, 495.

Calcii Acetylsalicylas (*B.P.C.* '34). $(\text{CH}_3\text{CO}\cdot\text{OC}_6\text{H}_4\cdot\text{COO})_2\text{Ca}, 2\text{H}_2\text{O}$ 434.2. Contains not less than 95% when assayed by weighing the sulphate formed on ignition with sulphuric acid.

Lithii Acetylsalicylas (*B.P.C.* '34). $\text{CH}_3\text{CO}\cdot\text{OC}_6\text{H}_4\cdot\text{COOLi}$ = 186.0. The lithium is assayed as Li_2SO_4 and should be equivalent to not less than 95% pure acetylsalicylate.

ACIDUM BENZOICUM

Acidum Benzoicum (*B.P.* '32). $\text{C}_6\text{H}_5\cdot\text{COOH}$ = 122.0. The natural and synthetic acids are official; at least 99.5% of free acid must be present and a limit test for chlorinated compounds is prescribed. M.p., 121° to 122° . The *U.S.P.* X acid after drying contains not less than 99.3%; the solution in dilute alcohol neutralised with phenolphthalein is titrated with standard barium hydroxide and a correction is applied for the proportion of chlorinated compound present. Both *Acidum benzoicum* and *Acidum benzoicum resina* are official in the *P. Helv. V*, the former melts at 120.5° to 121.5° and the latter between 118° and 121° .

Use as Preservative. Benzoic acid and sodium benzoate are not harmful if used in moderate amount. 0.1% is sufficient to preserve meat and butter, 0.05% is sufficient for fruit and fruit syrups.

Benzoic acid and benzoates may be used as preservatives in unfermented grape juice and non-alcoholic wine made from it, other sweetened or unsweetened non-alcoholic wines, cordials and fruit juices, sweetened mineral waters, brewer's ginger beer, coffee extract, and pickles and sauces made from fruit or vegetables. The proportions, calculated as parts of benzoic acid per million, must not exceed those specified in the Public Health (Preservatives, etc., in Food Regulations, 1925, *q.v.*

The antiseptic effect of benzoic acid in the small concentrations permitted is relatively low, and the resistance of yeasts varies within wide limits—the activity of some being suppressed by 0.03% to 0.05% while others resist 0.07% to 0.1%. A new yeast discovered in pear-juice, *Saccharomyces Lousozniensis*, resists 0.1% of sodium benzoate in glass vessels and 0.15% in presence of wood particles. It is killed at 65° —per *Yearb. Pharm.*, 1926, 329.

Detection in Foodstuffs. Extract with a mixture of ether and petroleum ether in equal parts; this evaporated may contain saccharin (taste), salicylic acid (by its colour with ferric chloride), and benzoic acid—recognised by odour, crystalline form, and conversion into aniline blue by heating with rosaniline and aniline.

COLORIMETRIC ESTIMATION IN CORDIALS, ETC. The aniline blue reaction is unsatisfactory, as acetic, succinic and salicylic acids also give the reaction. Best results with a modification of Halphen's Reaction, hydroxylamine hydrochloride being employed as reducing agent. Presence of benzoic acid indicated by fine red colour.—A. J. Jones, *Yearb. Pharm.*, 1925, 493.

Caution needed in search for traces of preservatives in caramel and boiled sugar sweets, which yield a crystalline acid substance (m.p. 122°), giving a violet colour with ferric chloride, similar to benzoic acid.—per *Yearb. Pharm.*, 1927, 185.

Determination in Foodstuffs (Fruits and Vegetables), in permitted amounts, specified under the Regulations in force since Jan. 1, 1927. A lengthy process, starting with steam distillation after saturating if necessary with salt, and subliming in presence of sand for 1 to $1\frac{1}{2}$ hours at 160° , and ultimately weighing the benzoic acid present.—G. W. Monier-Williams, *Rep. publ. Hlth med. Subj.*, No. 39, 1927, per *Yearb. Pharm.*, 1927, 182.

The application of Grossfield's modification of Mohler's test for benzoic acid to the detection and determination in foodstuffs is described. Details are given of the results obtained on various foods and the percentage errors are recorded for 31 different articles.—E. T. Illing, *Analyst*, 1932, 224.

Various methods of estimation of benzoates and salicylates.—E. B. R. Prideaux and A. O. Bentley.—*Pharm. J.*, i/1923, 427.

A distillation method of determination in foods (butter, margarine, and egg products) and in wines (not sweet).—per *Yearb. Pharm.*, 1927, 183. Also an adaptation of the French official method for detection in wines, showing 1 mg. in 100 ml. of wine.—*ibid.*, 1925, 149.

Ammonii Benzoas (*B.P.C.* '34). $C_6H_5 \cdot COONH_4 = 139 \cdot 1$. Contains not less than 98% and is assayed by adding excess of standard acid, separating the benzoic acid by means of ether and titrating the excess of acid with sodium hydroxide using phenol red as indicator. It is also official in the *U.S.P. X*, in which the salt dried over sulphuric acid contains 98% when assayed on its benzoic acid content separated with sulphuric acid and chloroform and the residue on evaporation titrated with barium hydroxide.

Lithii Benzoas (*B.P.C.* '34). $C_6H_5 \cdot COOLi = 128 \cdot 0$. Contains not less than 98.5% and is assayed by the B.P. process for sodium benzoate.

Sodii Benzoas (*B.P.* '32). $C_6H_5 \cdot COONa = 144 \cdot 0$. Moisture at 110° not more than 4% and the dried salt contains not less than 99% of the pure benzoate. The method of assay of the *B.P.* '14, in which the alkaline residue obtained on ignition was titrated, is replaced by the ether-acid process in which the alkali of a neutralised solution is titrated with standard sulphuric acid to bromophenol blue after removing most of the liberated benzoic acid with ether. Sodii Benzoas, *U.S.P. X*, by the ignition method after drying at 110° , contains not less than 99%.

Benzylis Benzoas (*B.P.C.* '34). $C_6H_5 \cdot COOCH_2 \cdot C_6H_5 = 212 \cdot 1$. The B.P. method for esters in essential oils with 2 hours boiling over a flame is used and a percentage of not less than 99 is required. Benzylis Succinas, *B.P.C.* '34, is required to have a purity of 99% and is assayed by the same method.

Ammonii Hippuras (*B.P.C.* '34). $C_6H_5 \cdot CO \cdot NH \cdot CH_2 \cdot COONH_4 = 196 \cdot 1$. This ammonium salt is readily soluble and should not contain any appreciable amount of free hippuric acid. When assayed for nitrogen by the Kjeldahl method it must contain the equivalent of not less than 98% of the pure hippurate.

Acidum Cinnamicum (*B.P.C.* '34). $C_6H_5 \cdot CH : CH \cdot COOH = 148 \cdot 1$. Determined in the same way as benzoic acid it is required to contain not less than 99%. Benzoic acid is tested for by titrating the filtrate obtained after shaking 1 g. with 100 ml. of boiled and cooled water at 20° for 1 hour, and must not exceed about 4%.

Coumarinum (*B.P.C.* '34). $C_9H_6O_2 = 146 \cdot 1$. Melts between 68° and 70° with limit of 0.05% for ash and test for absence of acetanilide and readily carbonisable matter.

Vanillinum (*B.P.C.* '34). 4-hydroxy-3-methoxybenzaldehyde, $CH_3O \cdot C_6H_3(OH) \cdot CHO$. Melts between 80° and 82° , with limit of 0.05% for ash and a

carbylamine test on 0.1 g. for absence of acetanilide. It is official in the *U.S.P. X* and the standard of purity is the same as that of the *B.P.C.*

“**Ethyl**” **Vanillin** (*m*-ethoxy-*p*-hydroxybenzaldehyde) has chemical properties very closely resembling those of vanillin and is four or five times stronger in flavour. It can be determined by a bromine absorption method.—H. C. Lockwood, *Analyst*, 1934, 730.

ACIDUM BORICUM

Acidum Boricum (*B.P.* '32). $\text{H}_3\text{BO}_3 = 61.84$. Contains not less than 99.5%, determined by titration with sodium hydroxide with the addition of glycerin, and phenolphthalein as indicator; it complies with a test for solubility in boiling alcohol. It is official in the *U.S.P. X* and should contain 99.5% of the pure substance after drying over sulphuric acid.

Detection of Boric Acid. See also *Milk Analysis*.

Boron compounds exist as normal constituents in cacao and cacao products in appreciable amounts—0.01% in chocolate, expressed as boric acid, and from 0.0217% to 0.0837% in commercial samples of cacao beans and cocoa. They also occur in small quantities (0.01%) in coffee beans. Samples of seaweed—Irish moss, seaweed (*Fucus*) and agar also contain traces, apparently as normal constituents.—per *Yearb. Pharm.*, 1927, 165. Also beans.—*ibid.*, 1926, 181.

Moisten congo red paper with a saturated aqueous solution and dry over a small flame; a blue colour is gradually developed. By using 1 in 1000 solution of congo red in a capsule and adding a little of a boric acid solution the presence of 0.00001 g. may be detected. The test is best applied to methyl or ethyl boric ester obtained by distillation.—per *Yearb. Pharm.*, 1925, 138.

The solution suspected to contain a borate is made slightly alkaline with sodium hydroxide and evaporated practically to dryness. The residue is treated with 1 ml. of concentrated sulphuric acid and cooled. 2 ml. of methyl alcohol is added and the mixture is transferred to a test tube fitted with a rubber stopper and two glass tubes. One of these extending to the bottom is bent at right angles and acts as a mouthpiece. The other conducts the vapours and is also bent, but drawn to a long capillary at least 3 cm. long and not more than 0.5 mm. bore. When air is blown through the apparatus the bubbles rising through the heated solution convey volatile methyl borate (if present), which tints a small bunsen flame a characteristic green colour.—A. Gabriel and H. G. Tanner, *J. Amer. chem. Soc.*, per *Chem. & Drugg.*, ii/1928, 777.

Manna can replace glycerin in the titration of boric acid.—L. E. Iles, *Analyst* 1918, 323.

Carbasus Acidi Borici (*B.P.C.* '34). Assayed by the process of the *B.P.C.* Shake in a stoppered bottle, a weighed quantity of the gauze (equivalent to about a quarter square yard) with 50 parts of boiled water and 40 parts of glycerin; cool and titrate with N/1 sodium hydroxide to phenolphthalein or phenol violet; from 10% to 20% of H_3BO_3 should be indicated.

Gossypium Acidi Borici (*B.P.C.* '34). Treated in the same manner as *Carbasus Acidi Borici* it contains from 15% to 30% of H_3BO_3 .

Borax (*B.P.* '32). $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O} = 381.4$. Assayed by the same method as boric acid, after neutralisation to methyl orange with sulphuric acid, it contains not less than 99% or more than the equivalent of 103% of $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O}$. *Sodii Boras*, *U.S.P. X*, contains 52.32% to 54.92% of the anhydrous salt corresponding to not less than 99% of the crystallised substance. *Borax*, *P.G. VI* contains 52.3% to 54.3% of anhydrous sodium tetraborate, $\text{Na}_2\text{B}_4\text{O}_7$.

French method recommended for testing official borax and other substance containing borates. Dissolve 1.91 g. of sample, finely powdered, by warming on water-bath in 25 ml. water and 50 ml. glycerin: solution complete in 30 minutes. When quite cold, titrate with N/1 NaOH with phenolphthalein as indicator. If pure, it will require exactly 10 ml. of N/1 NaOH.—per *Yearb. Pharm.*, 1927, 329.

Discovery in 1926 of enormous deposits of Kernite (or Rasorite), an entirely new mineral, in the Mohave Desert, Kern County, California, U.S.A. Kernite is virtually pure sodium borate, containing over 75% pure mineral with 25%

lay. For marketing, it is only necessary to dissolve in water, filter off the clay and recrystallise. Owing to the fact that 6 mols. of water are added to Kernite in the refining process to bring it up to commercial sodium borate (which contains 10 mols.), one ton of Kernite makes nearly a ton and a half of borax.—*Amer. J. Pharm.*, 1928, 480.

Sodii Perboras (*B.P.C.* '34). $\text{NaBO}_3 \cdot 4\text{H}_2\text{O} = 153.9$. Estimated by means of its oxidising action on potassium iodide in acidified solution and titration of the liberated iodine with sodium thiosulphate, it contains from 96% to the equivalent of 103% of $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$. *Sodii Perboras*, *N.F.V.*, by titration with potassium permanganate, contains 9% of available oxygen, corresponding to about 86.5% of $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$.

ASSAY, (*Fr. Cx. Supp.* II.). Dissolve 0.25 g. of the salt in 50 ml. of distilled water and 10 ml. of dilute sulphuric acid. Add to this solution sufficient solution of potassium permanganate (3.16 : 1000) to produce a permanent rose colour. For this purpose at least 28 ml. should be required, corresponding to 9% of active oxygen, or 86.5% of the pure salt.

Estimation of available oxygen in the perborate and in perborate soap powders. A volumetric method based on the reaction $\text{NaBO}_3 + \text{CaOCl}_2 + \text{H}_2\text{O} = \text{NaH}_2\text{BO}_3 + \text{CaCl}_2 + \text{O}_2$ found best.—H. Trickett, *Chem. & Drugg.*, 1920, 283.

ACIDUM CITRICUM

Acidum Citricum (*B.P.* '32). $\text{C}_3\text{H}_4(\text{OH})(\text{COOH})_3 \cdot \text{H}_2\text{O} = 210.1$. Assayed by titration with sodium hydroxide, using thymol blue as indicator, and should contain from 99.5% to the equivalent of 101% of the pure substance; limits of tartaric and oxalic acids are included. The *U.S.P. X* requires the same standard of purity but uses phenolphthalein as indicator for titration.

A method for the determination of citrate by oxidation with potassium permanganate in the presence of mercuric sulphate in which formates, tartrates, etc., do not interfere.—W. F. Bruce, *Ind. Engng Chem., Anal. Edn.*, 1934, 283.

Lithii Citras (*B.P.C.* '34). $\text{C}_6\text{H}_5\text{O}_7\text{Li}_3 \cdot 4\text{H}_2\text{O} = 281.9$. Should contain 98.5% of the pure salt; the assay by weighing the residue of Li_2SO_4 when ignited with sulphuric acid, replaces the *B.P.* '14 estimation of the alkalinity of the ash, by which method the *U.S.P. IX* salt also is estimated.

Potassii Citras (*B.P.* '32). $\text{C}_6\text{H}_5\text{O}_7\text{K}_3 \cdot \text{H}_2\text{O} = 324.3$. By titration of the ash with standard sulphuric acid it contains not less than 99% of $\text{C}_6\text{H}_5\text{O}_7\text{K}_3 \cdot \text{H}_2\text{O}$. Limit tests for alkalinity and acidity, tartrate and oxalate are included. The *U.S.P. X* salt is assayed similarly and after drying to constant weight over sulphuric acid contains 99%.

Sodii Citras (*B.P.* '32). $\text{C}_6\text{H}_5\text{O}_7\text{Na}_3 \cdot 2\text{H}_2\text{O} = 294.1$. Assayed by the same method as the potassium salt it is required to contain 99% of the pure substance. The *U.S.P. X* requires a purity of only 98%. Natrium citricum tribasicum, *P. Helv. V*, is the crystalline salt containing $5\frac{1}{2}$ molecules of water of crystallisation; by ignition and titration of the alkaline residue it should yield the equivalent of not less than 98% of $\text{C}_6\text{H}_5\text{O}_7\text{Na}_3 \cdot 5\frac{1}{2}\text{H}_2\text{O}$.

ACIDUM FORMICUM

Acidum Formicum (*B.P.C.* '34). Contains not less than 24% and not more than 26% *w/w* of $\text{H} \cdot \text{COOH}$ when assayed by digestion with alkaline potassium permanganate, the excess permanganate being titrated in acid solution with oxalic acid and a blank experiment made. Tests for the absence of acrolein and allyl formate and for limits of non-volatile matter and acetic acid are prescribed. *Acidum Formicum*, *N.F. V*, is of the same strength, when the total acidity is titrated with sodium hydroxide.

Acidum formicicum, *P.G. VI*, contains 24% to 25% of $\text{H}\cdot\text{COOH}$.
 Acidum formicicum, *P. Helv. V*, contains 24% to 25% *w/w* of $\text{H}\cdot\text{COOH}$.

Calcii Formas (*B.P.C. '34*). $(\text{H}\cdot\text{COO})_2\text{Ca} = 130\cdot1$. Determined by the same method as formic acid it should contain not less than 98% of the pure substance.

Potassii Formas (*B.P.C. '34*). $\text{H}\cdot\text{COOK} = 84\cdot10$. Estimated for formate content, equivalent to 95% of $\text{H}\cdot\text{COOK}$.

Sodii Formas (*B.P.C. '34*). $\text{H}\cdot\text{COONa}, \text{H}_2\text{O} = 86\cdot02$. Assayed by the method for calcium formate, it contains not less than 96%.

ACIDUM GLYCEROPHOSPHORICUM

Acidum Glycerophosphoricum (*B.P.C. '34*). Contains 19% to 21% *w/w* of $\text{C}_3\text{H}_9\text{O}_6\text{P}$; limit of combined alkali (as Na_2O), 0.5%; limit of free phosphate (as P_2O_5), 0.5%. Assayed by the *B.P.C. '34* process by titration with normal sodium hydroxide to bromocresol green and titration with sodium hydroxide to thymol blue, followed by boiling with neutralised calcium chloride solution and further titration to thymol blue, the latter indicating free phosphoric acid present; the difference between the first thymol blue titration and twice the bromocresol green indicates the combined alkali present, and the first thymol blue titration less the free phosphate and the bromocresol green titration represents the glycerophosphoric acid, calculated on the neutralisation of one H ion. Free glycerin is determined by separating the glycerophosphate as calcium salt from alcoholic solution, evaporating and drying the filtrate, and should not exceed 2%.

The analysis of glycerophosphate syrups.—G. Middleton, *Yearb. Pharm.*, 1926, 421.

The alkali and alkaline earth salts of glycerophosphoric acid on the English market are for the most part perfectly definite salts and of reasonable purity. The most noticeable difference between the products of different manufacturers is the considerable variation in the amount of water of crystallisation, especially in the magnesium and 50% sodium salts. The majority are not adjusted to a basis of 50% of anhydrous salt. The 50% potash salt appears to be.—G. J. W. Ferrey, *Yearb. Pharm.*, 1926, 481.

Calcii Glycerophosphas (*B.P.C. '34*). $\text{CaC}_3\text{H}_5(\text{OH})_2\text{PO}_4, 2\text{H}_2\text{O} = 246\cdot2$. Loses not more than 15% of its weight at 130° and then contains not less than 98% of the anhydrous salt, determined by ignition to pyrophosphate. Yields not more than 1% of residue (glycerin, etc.) insoluble in dehydrated alcohol; limits of alkalinity or acidity, citrate and glycerin and minimum of glycerophosphate are prescribed. The *U.S.P. X* allows a loss of only 10% at 130° and is then of the same strength; assayed by ignition to pyrophosphate and by precipitation of the calcium as oxalate and subsequent ignition to oxide. Calcium glycerino-phosphoricum, *P.G. VI*, contains not less than 84% of anhydrous calcium glycerophosphate. Calcium glycerinophosphoricum, *P. Helv. V*, contains not more than 16% of moisture, not less than 84% of $\text{C}_3\text{H}_7\text{O}_6\text{PCa}$, determined by dissolving in normal hydrochloric acid and titrating back with sodium hydroxide to methyl orange, and from 50.6% to 55.5% of ash on ignition.

Ferri Glycerophosphas (*B.P.C. '34*). Assayed for Fe content by titration of the liberated iodine, after interaction with potassium iodide, with sodium thiosulphate, contains from 13% to 16% of Fe. Residue on ignition, not less than 42%. Ferri Glycerophosphas, *N.F. V*, contains Fe $(\text{C}_3\text{H}_7\text{O}_6\text{P})_3$ equivalent to 14% to 16% of Fe.

Magnesii Glycerophosphas (*B.P.C. '34*). $\text{MgC}_3\text{H}_5(\text{OH})_2\text{PO}_4, 2\text{H}_2\text{O} = 230\cdot4$. Loses not more than 16% at 130° ; and then contains not less than 97% of $\text{C}_3\text{H}_7\text{O}_6\text{PMg}$, as estimated by weight of the ignited residue of pyrophosphate. Similar limit tests to those for the calcium salt are described.

Mangani Glycerophosphas (*B.P.C.* '34). $\text{MnC}_3\text{H}_5(\text{OH})_2\text{PO}_4 = 225.0$. By calculation from the weight of the ignited residue the substance dried at 130° contains not less than 97% . Loss at 130° not more than 5% . Tests for limit of citrate, glycerin, alkalinity or acidity, and minimum of glycerophosphate are included. **Mangani Glycerophosphas Solubilis**, *N.F. V*, contains 70% to 75% of the salt rendered soluble with citric acid; assayed by precipitation as sulphide and ignition to Mn_3O_4 .

Potassii Glycerophosphas Liquidus (*B.P.C.* '34). Determined by the same methods as **Sodii Glycerophosphas**, it complies with the same limits for free alkali, free phosphate and glycerin and contains 48% to 52% *w/w* of $\text{C}_3\text{H}_7\text{O}_6\text{PK}_2, 3\text{H}_2\text{O}$. Sp. gr., 1.38 to 1.42.

Sodii Glycerophosphas (*B.P.C.* '34). $\text{C}_3\text{H}_7\text{O}_6\text{PNa}_2, 5\frac{1}{2}\text{H}_2\text{O} = 315.2$. Contains not less than 98% and not more than the equivalent of 102% of the pure substance with free alkali limit (as Na_2CO_3) of 0.5% and a free phosphate limit (as P_2O_5) of 0.5% . Assayed by the method of the *B.P.C.* by titration with normal hydrochloric acid using bromocresol green as indicator, less the sum of the readings for free alkali and free phosphate; these being obtained by titration with normal hydrochloric acid to thymol blue (free alkali) and subsequent addition of neutralised calcium chloride solution, boiling, and further titration of the cooled liquid with normal sodium hydroxide to thymol blue (free phosphate). The *N.F.V* substance contains 68% of the anhydrous salt, as shown by titration with hydrochloric acid to methyl orange.

Sodii Glycerophosphas Liquidus (*B.P.C.* '34). A solution of sp. gr. 1.28 to 1.32 containing 48% to 52% by weight of $\text{C}_3\text{H}_7\text{O}_6\text{PNa}_2, 5\frac{1}{2}\text{H}_2\text{O}$; free alkali (as Na_2CO_3) and free phosphate (as P_2O_5) limits, 0.5% . Assayed by the same process as for **Sodii Glycerophosphas**. Limit of free glycerin, determined by shaking with four volumes of dehydrated alcohol and one part of recently ignited calcium sulphate, filtering and evaporating the filtrate and alcoholic washings, and drying at 70° for one hour, 2% . Refractive index, 1.395 to 1.405.

ACIDUM HYDRIODICUM

Acidum Hydriodicum Dilutum (*B.P.C.* '34). Contains 9.8% to 10.2% *w/w* of HI, replacing the limits of the *B.P.* '14, approximately 9.7% to 10.2% , and a sulphate limit is included. Assayed by addition of excess silver nitrate solution and titration with ammonium thiocyanate. The *U.S.P. X* acid contains from 9.5% to 10.5% of HI and a test for free iodine is included.

Ammonii Iodidum (*B.P.C.* '34). $\text{NH}_4\text{I} = 145.0$. The salt dried at 100° contains 98% , 5% loss on drying at 100° being allowed. Assayed by the *B.P.* process for potassium iodide by titration with potassium iodate in presence of hydrochloric acid.

Calcii Iodidum (*B.P.C.* '34). $\text{CaI}_2 = 293.9$. Determined by iodide content it contains not less than 80% of CaI_2 .

Lithii Iodidum (*B.P.C.* '34). $\text{LiI} = 133.9$. Loses not more than 10% at 120° and the dried salt contains 99% of LiI. The iodide may be estimated by titration with standard potassium iodate.

Potassii Iodidum (*B.P.* '32). $\text{KI} = 166.0$. The dried salt contains 99% of KI. Titration with M/20 potassium iodate in presence of not less than 40% of hydrochloric acid replaces the *B.P.* '14 determination with silver nitrate solution; moisture is now determined at 110° and should not exceed 1% . The *U.S.P. X* salt contains 99% of KI after drying at 100° , and is assayed by the general method for iodides by addition of silver nitrate and back titration with potassium thiocyanate.

Alternative Assay Process. The following assay process based on the formation of iodine cyanide is preferable to that of the *B.P.* The potassium iodide solution, containing about 0.5 g. in 50 ml. of water, is strongly acidified with hydrochloric acid and treated with potassium cyanide solution. The mixture is then titrated with M/40 potassium iodate, using starch mucilage as indicator, until the last trace of blue or reddish violet colour has disappeared. Each millilitre of M/40 potassium iodate is equivalent to 0.0083 g. of KI.

This method can also be applied to solutions containing iodine and potassium iodide. 5 ml. of approximately N/10 iodine is diluted to about 100 ml. and treated with 50 ml. of 2N hydrochloric acid and 5 ml. of 10% potassium cyanide. The mixture is then titrated with M/40 potassium iodate until the colour disappears. Excess of potassium iodide is then added and the liberated iodine titrated with thiosulphate. If the two titrations are a and b ml. respectively the potassium iodide is given by the expression $\frac{166.02 (5a - 2b)}{200}$ g. per litre

and the iodine is given by the expression $\frac{126.92 (2b - 3a)}{100}$ g. per litre

—A. D. Mitchell, Lecture to Institute of Chemistry, 19/10/1934.

Sodii Iodidum (*B.P.* '32). $\text{NaI} = 149.9$. Loses not more than 5% at 110° and then contains 99% of the pure salt. There is no change in standard from the *B.P.* '14 but the silver nitrate titration is again replaced with potassium iodate. The *U.S.P. X* allows 7% of water loss at 120° and the salt should then be of 99% purity, assayed by the general method for iodides.

Strontii Iodidum (*B.P.C.* '34). $\text{SrI}_2 \cdot 6\text{H}_2\text{O} = 449.6$. Titrated with standard iodate solution, it contains 99% of the hydrated substance.

Zinci Iodidum (*B.P.C.* '34). $\text{ZnI}_2 = 319.2$. Contains not less than 98% of the pure salt, assayed for its iodide content.

ACIDUM HYDROBROMICUM

Acidum Hydrobromicum (*B.P.C.* '34). Contains 34% to 35% *w/w* of HBr and has sp. gr. of 1.303 to 1.314. 290 g. with 710 g. of water produces an acid of approximately the same strength as Acidum Hydrobromicum Dilutum, *B.P.* '32, containing 9.8% to 10.2% of HBr and with a sp. gr. of 1.072 to 1.075. A limit of chlorine equivalent to about 0.12% of HCl is included. Acidity estimated with standard sodium hydroxide to methyl orange.

Ammonii Bromidum (*B.P.C.* '34). $\text{NH}_4\text{Br} = 97.96$. Loses not more than 1% at 100° and then contains 99% of the pure salt. The *B.P.* '14 required only 98% purity with the same moisture allowance. Estimated by total halogen content, with chloride and bromate limits specified. The *U.S.P. X* salt contains 98.5% of NH_4Br , after drying 24 hours over sulphuric acid. Ammonium bromatum, *P.G. VI*, dried at 100° , contains at least 98.8% of NH_4Br .

Calcii Bromidum (*B.P.C.* '34). $\text{CaBr}_2 \cdot 2\text{H}_2\text{O} = 235.9$. Contains not less than 98% of the pure salt, assayed as Potassii Bromidum. Calcii Bromidum *U.S.P. X*, contains 84% of the anhydrous salt which is equivalent to approximately 99% of the hydrated compound.

Lithii Bromidum (*B.P.C.* '34). $\text{LiBr} = 86.86$. By titration with excess of silver nitrate and ammonium thiocyanate the dried salt contains 98% of LiBr. Loss at 160° , not more than 15%. Tests for limit of bromate and iodide are included. Lithii Bromidum, *N.F. V*, contains 85% of the anhydrous salt after drying for 24 hours over sulphuric acid; a limit of "other alkalis," by weighing the chlorides insoluble in amyl alcohol, is included.

Potassii Bromidum (*B.P.* '32). $\text{KBr} = 119.0$. A purity of 99% on the dried substance replaces the 98% *B.P.* '14 salt and the limit of 1% of moisture is not determined at 110° . Assayed by addition of excess silver nitrate and back titration with ammonium thiocyanate. It is official in the *U.S.P. X* when the salt dried at 100° should contain 98.5% of KBr.

Fluorescein Test for Bromine in Body Fluids. Soak strips of filter paper in a saturated solution of fluorescein in 60% acetic acid, and allow to dry. Add to body fluid in a test tube a few crystals of potassium permanganate. Agitate and add a few drops of concentrated sulphuric acid. Moisten fluorescein paper with 2% acetic acid and hold at mouth of test-tube. Presence of bromine indicated by rapid change of paper from yellow to bright pink. Presence of chlorine and iodine does not interfere with test. Found positive in urine voided 15 minutes after oral administration of 10 grains of sodium bromide. The fluorescein papers will keep.—G. H. Belote, *J. Amer. med. Ass.*, i/1927, 1697.

A method for the estimation of bromides in urine in the presence of large amounts of chlorides.—G. H. W. Lucas, *J. Pharmacol.*, 1928, 223.

Cushny found that after a single dose of 30 grains of bromide the urine may contain traces of the drug for 2 months, only about 10% being eliminated in the first 24 hours.—J. H. Hannan, *Practitioner*, ii/1927, 262.

Sodii Bromidum (*B.P.* '32). $\text{NaBr} = 102.9$. Loss on drying at 110° not more than 5% and then contains 99% of the pure salt, assayed for bromide content. The *U.S.P. X* requires the substance dried at 100° to contain 98.5% of NaBr and no limit of moisture is prescribed.

Strontii Bromidum (*B.P.C.* '34). $\text{SrBr}_2 \cdot 6\text{H}_2\text{O} = 355.6$. Assayed by the same method as Potassii Bromidum. It should contain not less than 97% of the pure substance. The *B.P.* '14 required the residue on ignition with sulphuric acid to correspond to 97% purity also.

Zinci Bromidum (*B.P.C.* '34). $\text{ZnBr}_2 = 225.2$. Contains not less than 95% of ZnBr_2 . Assayed by the *B.P.* process for Zinci Sulphas as follows:—Dissolve about 0.5 g. in 120 ml. of water, acidify with a drop of dilute sulphuric acid, add 25 ml. of mercuric ammonium thiocyanate solution, allow to stand for 5 minutes, stir well and stand for a further hour; filter on a small suction filter and wash with five quantities of 10 ml. of mercuric ammonium thiocyanate solution, diluted with water (1 : 50). To the precipitate and filter in a stoppered bottle add 40 ml. of hydrochloric acid and titrate with *M*/5 potassium iodate, using 5 ml. of chloroform as indicator.

ACIDUM HYDROCHLORICUM

Acidum Hydrochloricum (*B.P.* '32). Contains from 31% to 33% by weight of HCl ; sp. gr., 1.156 to 1.168. Acidum Hydrochloricum Dilutum contains from 9.5% to 10.5% of HCl and has a sp. gr. of 1.045 to 1.052. The corresponding acids of the *U.S.P. X* are of the same strengths with sp. gr. of about 1.155 and 1.049 respectively at 25° . Acidum hydrochloricum fortius and Acidum hydrochloricum dilutum, *P. Helv. V*, should contain respectively 24.9% to 25.1% and 9.9% to 10.1% *w/w* of HCl . Acidum Hydrochloricum, *P.G. VI*, contains 24.8% to 25.2% of HCl and Acidum hydrochloricum dilutum 12.4% to 12.6%.

Ammonii Chloridum (*B.P.* '32). $\text{NH}_4\text{Cl} = 53.5$. Loses not more than 1% when dried in a vacuum desiccator over sulphuric acid for 24 hours and should then contain 99.5% of NH_4Cl . Residue on volatilisation not more than 0.1%. Assayed on the chloride content by addition of excess standard silver nitrate to a solution acidified with nitric acid and adjustment to volume, followed by titration of an aliquot part with ammonium thiocyanate using ferric ammonium sulphate as indicator. The salt is official in the *U.S.P. X* and is of the same strength.

The *B.P.* assay takes a longer time than a direct method and the use of dichloro-fluorescein as adsorption indicator is preferable.—E. J. Shorn and J. Y. Baird, *Pharm. J.*, i/1934, 361.

Calcii Chloridum (*B.P.* '32). $\text{CaCl}_2 = 111.0$. The salt of 98% purity after drying at 200° , when the loss should be not more than 10%, replaces the unstandardised salt of the *B.P.* '14, with 5% moisture allowance. Assayed by titration with standard silver nitrate using potassium chromate as indicator. Calcii Chloridum, *U.S.P. X*, is only required to be of 75% purity.

Lithii Chloridum (*B.P.C.* '34). $\text{LiCl} = 42.40$. Loses, on drying at 100° , not more than 5% of its weight and then contains 99% of LiCl by titration of the chloride.

Magnesii Chloridum (*B.P.C.* '34). $\text{MgCl}_2 \cdot 6\text{H}_2\text{O} = 203.3$. 2 g. yields a clear solution in 10 ml. of alcohol (85%); CaSO_4 limit, 4%, determined by dissolving in 25 parts of 20% sulphuric acid, adding 50 parts of 95% alcohol and allowing to stand overnight. Magnesii Chloridum, *N.F. V*, contains 95% of the hydrated salt after drying for 24 hours over sulphuric acid, determined on its chloride content.

Potassii Chloridum (*B.P.C.* '34). $\text{KCl} = 74.55$. Titrated by the method for Sodii Chloridum, the substance dried at 130° contains 99.5% of KCl . Loses not more than 1.0% at 130° .

Sodii Chloridum (*B.P.* '32). $\text{NaCl} = 58.45$. Loses not more than 1.0% at 130° and then contains 99.5% of the pure salt. A test for the absence of iodides and bromides, by the addition of chloroform and chlorine solution to the alcohol-soluble matter dissolved in water, is included. The *U.S.P. X* salt contains 99% of NaCl after drying at 110° .

The Food and Drug Administration of the U.S. Dept. of Agriculture define table salt, dairy salt, as fine-grained crystalline salt containing, on a water-free basis, not more than 0.5% of calcium and magnesium chlorides, nor more than 0.1% of matter insoluble in water. Pending further announcement, no exception is taken to content of anhydrous calcium sulphate (anhydrite) in excess of 0.1% provided the total calcium sulphate content does not exceed 1.4%.—*S.R.A., F.D. No. 2, Rev. 4, Aug. 1933.*

Zinci Chloridum (*B.P.* '32). $\text{ZnCl}_2 = 136.3$. Assayed by precipitation of the solution acidified with sulphuric acid with mercuric ammonium thiocyanate, and titration in hydrochloric acid of the washed precipitate with standard potassium iodate, using chloroform as indicator, it contains zinc equivalent to 95% of ZnCl_2 . No assay or standard of purity was included in the *B.P.* '14. The *U.S.P. X* salt is of the same strength, determined by titration of its chloride content, or electrolytically.

Perchloric Acid, HClO_4 . Available commercially containing 60% *w/w*, with sp. gr. 1.54. A powerful acid and oxidising agent. As a reagent for potassium, qualitatively and quantitatively, it has largely replaced the chloroplatinate method.

ACIDUM HYDROCYANICUM

Acidum Hydrocyanicum Dilutum (*B.P.* '32). Contains 1.9% to 2.1% *w/w* of HCN . Acidum Hydrocyanicum Fortius (*B.P.C.* '34) contains 3.8% to 4.2% of HCN , and the dilute acid of the International Agreement, 2%. Determined by titration with silver nitrate in ammoniacal solution using potassium iodide as indicator.

The official method gives practically the same percentage as the old soluble double salt $\text{AgNa}(\text{CN})_2$ method. The presence of chloride makes no appreciable difference. Excess of alkali causes only a slight error.—D. B. Dott, *Pharm. J.*, i/1916, 368.

Determination of hydrocyanic acid.—C. E. Corfield and C. J. Eastland, *Yearb. Pharm.*, 1921, 391.

For Waller's and Walden's methods see previous edition.

Delicate Test for Hydrocyanic Acid. A few drops of phenolphthalin solution made alkaline with sodium hydroxide added to liquid to be tested. If red colour be produced on adding cupric sulphate solution 1 in 2000 (due to oxidation into phenolphthalein) hydrocyanic acid is proved to be present. Phenolphthalin is made by reducing phenolphthalein with zinc in alkaline solution.—*Pharm. J.*, i/1905, 721.

Place 1 drop of 1 : 5 ammonia dilution on a microscopic slide and invert over tube containing the solution to be tested, together with a few drops of sulphuric acid. After a few minutes remove slide and place under microscope: on the addition of 1 drop of alloxan solution (made by boiling 0.1 g. of uric acid with 0.2 ml. of nitric acid and 0.2 ml. of water and diluting to 5 ml.) crystals of oxaluramide begin to form in a few minutes if the test solution contains a cyanide. Substitution of pyridine for ammonia renders test far more delicate so that a few drops of a solution containing 0.01 g. HCN per litre gives positive results.—per *Yearb. Pharm.*, 1927, 168.

As a bactericide (fumigant in ship disinfection) hydrocyanic acid is too weak to affect pathogenic germs. It has no measurable carbolic acid co-efficient. Less than 0.02.—W. C. Reynolds, *Lancet*, ii/1922, 834. Its danger.—*Pharm. J.*, i/1923, 300. It destroys rats, fleas, etc. It has no ill effects on dry grain, but moist food, e.g., butter, milk, etc., is liable to absorb the gas.

To destroy bugs hydrocyanic acid is much used in S. Africa. Stringent regulations control its use and the licensing of disinfectors employed.—J. Porter, *Lancet*, ii/1921, 583.

While a concentration of 2 g. of HCN per ml. of air will kill an animal in a few minutes, animals given a previous dose of glucose, by injection or by the mouth, can breathe this atmosphere for more than an hour without ill effects.—*Lancet*, ii/1926, 94.

Its use as a fumigant should be universally prohibited. Two deaths in Lausanne following its use for destruction of bugs. Risk of retention of the gas in water, moisture, bedding, cushions, hangings, and foodstuffs.—F. M. Lesserli, per *Lancet*, ii/1932, 799.

Deaths of two children at Aldershot after fumigation of house more than 4 hours previously, in spite of application of usual precautions. Ministry of Health should be given statutory power to make regulations for the control of fumigation with poisonous gases.—*Lancet*, i/1935, 1065.

Insecticides.—The specification of the Association of British Insecticide Manufacturers (Bulletin No. 82, Ministry of Agriculture and Fisheries) requires **Potassium Cyanide** to contain not less than 93% potassium cyanide: **Sodium Cyanide** to contain not less than 97% sodium cyanide: **Calcium Cyanide** to contain not less than 40% calcium cyanide. The strength of sodium cyanide is frequently expressed in terms of potassium cyanide; thus 97% to 98% sodium cyanide may be referred to as 129% to 130% cyanide.

Aqua Laurocerasi (*B.P.C.* '34). Adjusted to contain 0.09% to 0.11% *w/v* of HCN and assayed by the method for Acidum Hydrocyanicum Dilutum. Aqua laurocerasi I.A. and Aqua Amygdalæ Amaræ I.A. each contain 0.1% of HCN.

It has been held that the method of preparation in the *Fr. Cx.* is impracticable. The *Fr. Cv.* assumes a content of 0.12% to 0.16% of HCN in the leaves. They never yield 0.10%. The previous *Fr. Cx.* formula was only half this strength, *z.*, 0.05%. If the leaves are well crushed or disintegrated, not used entire or merely cut, the content of HCN in the water may be 1.5 to 1.7 per 1000.

The bright green young *Prunus Laurocerasus* leaves were found to yield from two to four times the amount of hydrocyanic acid given by the older and more leathery brown leaves of cherry laurel. Adequate manuring caused increase in the amount of hydrocyanic acid contained.—D. H. Wester, *Pharm. J.*, 1904, 643.

Oleum Amygdalæ Amaræ (*B.P.C.* '34). Contains not less than 85% *w/w* of C_6H_5CHO and the equivalent of 2% to 4% *w/w* of HCN. Sp. gr., 1.055 to 1.065. Refractive index at 20°, 1.534 to 1.542. Assayed by the *B.P.C.* method for benzaldehyde, in which standard hydroxylamine hydrochloride is added to the oil, and titrated with N/2 alcoholic potassium hydroxide, using methyl orange as indicator, allowance being made for the free benzoic acid present. Hydrocyanic acid is determined by titration of the alcoholic solution, made slightly ammoniacal, with standard silver nitrate to a permanent opalescence with potassium iodide. A benzoic acid limit, equivalent to approximately 2%, is included and the oil should comply with the *B.P.C.* limit test for chlorinated compounds in Benzaldehydum. Nitrobenzene is tested for by reduction of an alcoholic solution with zinc powder and acetic acid, the presence of any aniline formed being detected by the odour of phenyl isocyanide on warming the mixture with chloroform and excess of sodium hydroxide. The *U.S.P. X* requires a sp. gr. of 1.038 to 1.06 at 25° and the same strengths of benzaldehyde and hydrocyanic acid; the former is assayed by interaction with phenylhydrazine solution, addition of excess of half-normal hydrochloric acid, filtration and washing of the precipitated hydrazone, and back titration of the filtrate with standard sodium hydroxide to methyl orange, a blank titration being performed on the phenylhydrazine solution; hydrocyanic acid is titrated with silver nitrate, using potassium chromate as indicator, in presence of magnesium sulphate and sodium hydroxide. Nitrobenzene is tested for by reduction to aniline as in the *B.P.C.*

The Food and Drug Administration of the U.S. Dept. of Agriculture define oil of bitter almonds, commercial, for food purposes, as the volatile oil from the seed of the bitter almond (*Amygdalus communis* L.), the apricot (*Prunus armeniaca* L.), or the peach (*Amygdalus persica* L.)—*S.R.A., F.D. No. 2, Rev. 4* Aug., 1933.

In America, benzaldehyde is largely substituted for oil of bitter almonds.

Frequently hydrocyanic acid in sufficient quantity is added to meet the requirements of the trade or the *U.S.P.* Adulteration with benzaldehyde can only be detected if the synthetic benzaldehyde contains chlorine. For method of assay see Salamon, *Perfum. essent. Oil Rec.*, 1917, 41. Much of the synthetic benzaldehyde is now produced by processes which do not involve the use of chlorine and is therefore free from that impurity. Benzaldehyde is considered to be inferior as a flavouring agent to natural oil of bitter almonds.

Benzaldehyde is liable to spontaneous ignition if badly packed, e.g., in leaky tins surrounded with wood shavings, or on filter paper.—*Yearb. Pharm.*, 1925, 54, 55.

Oleum Amygdalæ Amaræ sine Acido Hydrocyanico (*B.P.C.* '34). Estimated by the method for Benzaldehydum, should contain 95% by weight of C_6H_5CHO . Sp. gr., 1.048 to 1.052. Refractive index at 20°, 1.540 to 1.545. Limits for benzoic acid and nitrobenzene as for Oleum Amygdalæ Amaræ, and should not contain any hydrocyanic acid as shown by addition of sodium hydroxide and ferrous sulphate and acidification with hydrochloric acid, when no greenish blue colour or precipitate is produced. Complies with the test for chlorinated compounds in Benzaldehydum.

ACIDUM HYPOPHOSPHOROSUM

Acidum Hypophosphorosum (*B.P.C.* '34). Contains 30% to 32% of H_3PO_2 . 323 g. with 677 g. of water yields an acid of approximately the same strength as Acidum Hypophosphorosum Dilutum, *B.P.* '32, 9.8% to 10.2% w/w of H_3PO_2 . The *U.S.P.* X acid is of the same strength as the *B.P.C.* acid.

The *B.P.* limits for chlorides, sulphates, iron, arsenic and lead are unnecessarily stringent.—*Pharm. J.*, ii/1932, 47.

Determination of Phosphorus in Syrups.—An amount of material corresponding to from 15 to 20 mg. of P_2O_5 is dissolved in 70 ml. of water, 5 ml. of nitric acid is added and 10 g. of ammonium nitrate, and the temperature raised to 65°. To the stirred solution is then added, in a thin stream, 35 ml. of nitric acid solution of ammonium molybdate. The mixture is stirred for a further 30 seconds allowed to stand at a temperature of 65° to 70° for 15 minutes, removed from the water-bath and allowed to cool for a further 15 minutes, the supernatant liquid being then filtered off through an asbestos or paper pulp filter in a Gooch crucible under slight suction. The precipitate is washed, as far as possible by decantation, with two 20 ml. portions of 5% nitric acid, then with five 20 ml. portions of 5% ammonium nitrate solution, and finally with small quantities of water. The final washings should not redden litmus paper. The precipitate is transferred to the original beaker, the crucible being washed out with about 50 ml. of water, 50 ml. of N/5 sodium hydroxide (free from carbonate) is added, the yellow precipitate allowed to dissolve completely, and the excess of alkali titrated with N/5 hydrochloric acid, using thymol blue or phenol violet as indicator and titrating to the yellowish-green tint.—G. J. W. Ferrey, *Quart. J. Pharm.*, 1934, 347.

Calcii Hypophosphis (*B.P.C.* '34). $CaP_2H_4O_4 = 170.2$. Assayed by digestion in the dark for 12 hours with sulphuric acid and standard iodine solution and back titration with thiosulphate, it contains 98% of the pure substance; phosphorus insoluble in water, not more than 0.5%. The *N.F. V* substance is assayed by dissolving in 10 ml. of water and evaporating with two quantities of 10 and 5 ml. of nitric acid, again dissolving, and diluting to 100 ml.; neutralising a portion of this solution, representing about 0.075 g., with sodium hydroxide and an excess of N/10 silver nitrate, shaking, and adding zinc oxide until neutral to litmus; diluting to known volume and back titrating an aliquot part with potassium thiocyanate, using iron alum as indicator; the substance dried over sulphuric acid should contain 98% of $Ca(H_2PO_2)_2$.

Ferri Hypophosphis (*B.P.C.* '34). $Fe(H_2PO_2)_3 = 250.9$. Contains from 97% to the equivalent of 101% of $Fe(H_2PO_2)_3$, after drying at 100°, when it loses not more than 5%. Assayed by the *B.P.C.* '34 method by digestion with potassium iodide and N/10 iodine in presence of hydrochloric acid in the dark for 4 hours, followed by back titration with N/10 sodium thiosulphate, where

the iodine liberated by the ferric radicle less that used in oxidation of the hypophosphorous acid is titrated. Ferri Hypophosphis, *N.F. V*, is estimated for Fe content only by evaporation with nitro-hydrochloric acid, interaction with potassium iodide in acid solution and titration of the liberated iodine, a Fe content of 21·8% being indicated, equivalent to 98% of the pure substance.

Mangani Hypophosphis (*B.P.C.* '34). $\text{Mn}(\text{H}_2\text{PO}_2)_2 \cdot \text{H}_2\text{O} = 203\cdot0$. Estimated by hypophosphite content a purity of not less than 97% is required. As indicated by treatment with nitric acid and finally titrating the neutralised solution with silver nitrate and potassium thiocyanate, the *N.F. V* salt is of the same purity.

Potassii Hypophosphis (*B.P.C.* '34). $\text{KH}_2\text{PO}_2 = 104\cdot1$. Assayed by the *B.P.C.* method for Calcii Hypophosphis it contains 98% of KH_2PO_2 , after drying over sulphuric acid. Loses not more than 2% on drying over sulphuric acid. Insoluble phosphate limit, 0·5%. Potassii Hypophosphis, *N.F. V*, assayed by evaporation with nitric acid, precipitation in neutral solution with silver nitrate and back titration with potassium thiocyanate, contains 98% of KH_2PO_2 after drying over sulphuric acid, but no limit of moisture is specified.

Sodii Hypophosphis (*B.P.C.* '34). $\text{Na}_2\text{HPO}_2 = 88\cdot03$. By the assay process for Calcii Hypophosphis it contains 97% of the pure substance, calculated to the dry substance, a loss of 2% being allowed at 110°. Sodii Hypophosphis, *N.F. V*, is the hydrated substance, $\text{NaH}_2\text{PO}_2 \cdot \text{H}_2\text{O}$, of which it should contain 98%.

ACIDUM LACTICUM

Acidum Lacticum (*B.P.* '32). Contains the equivalent of not less than 87·5% *w/w* of $\text{C}_3\text{H}_6\text{O}_3$; it is assayed to include both lactic acid and lactide, by boiling for five minutes with excess of normal sodium hydroxide and back titration with sulphuric acid to phenolphthalein, a blank titration being made. Sp. gr. about 1·21. A test for limit of various reducing sugars is included as shown by the formation of not more than a slight red precipitate on boiling the neutralised acid with Fehling's solution. The acid of the *B.P.* '14 contained 75% of hydrogen lactate with 10% of lactide. Lactic acid, *U.S.P. X* contains the equivalent of 85% to 90%; also assayed with excess of sodium hydroxide but with boiling for twenty minutes. The *P.G. VI* requires (with sp. gr. 1·206 to 1·216) total acid 90%, of which about 72% is free acid, reckoned as lactic acid. Assay process: 5 g. of lactic acid is diluted with water to 100 ml. 40 ml. of this mixture is neutralised with N/1 KOH in presence of phenolphthalein, using approx. 16 ml. of test solution (=72% of lactic acid). Further 5 ml. of N/1 KOH is added and the mixture warmed 5 minutes on the water-bath until the pink colour of phenolphthalein has disappeared. Then 2 ml. of N/1 HCl is added with further 2 minutes warming. The excess acid is back titrated. The total N/1 KOH used less the total N/1 HCl must be approx. 20 ml., i.e., approx. 90% total acid. Acidum Lacticum Dilutum, *B.P.C.* contains about 15% by volume of lactic acid and has a sp. gr. of about 1·04

The absence from the *B.P.* of any limit for lactide is a disadvantage if the acid is used for the preparation of Calcii Lactas Recens.—*Ret. Chem.*, ii/1932, 271.

Detection of Lactic Acid. A bright red colouration is obtained when 0·2 ml. of solution, containing less than 0·2% of lactic acid, is heated for two minutes at 100° with 2 ml. of conc. H_2SO_4 , cooled and treated with two drops of 5% alcoholic guaiacol solution.

This reaction is not given by formic, acetic, malic, benzoic or salicylic acids. Citric acid gives a yellow colour, tartaric acid a slight red colour, and tannin a blackish-violet.—*J. chem. Soc. Abstr.*, ii/1921, 356.

Calcii et Sodii Lactas (*B.P.C.* '34). $C_{12}H_{20}O_{12}CaNa_2 \cdot 4H_2O = 514.3$. Loses not more than 16% of its weight at 130° , and then contains 8.5% to 9.5% of Ca and 10% to 11% of Na. A free acid limit equivalent to approximately 0.9% of lactic acid is included. Calcium is determined gravimetrically, by precipitation as oxalate and titration with sulphuric acid of the ignited residue; titration of the total alkalinity of the ash, less the titration for calcium, is calculated to Na.

Calcii Lactas (*B.P.* '32). $C_6H_{10}O_6Ca \cdot 5H_2O = 308.2$. As indicated by weight of the sulphated residue, it contains from 97% to the equivalent of 103% of the pure substance. The *B.P.* '14 required a purity of only 93% and a test for limit of various sugars was not included. **Calcii Lactas**, *U.S.P.X.*, contains from 70% to 75% of the anhydrous substance, equivalent to not less than 98% of the hydrated salt, determined on the residue dried at 120° , by dissolving the ignited residue in half normal hydrochloric acid and back titrating with standard sodium hydroxide. Calcium lacticum, *P.G. VI*, contains 70.5% to 73% of anhydrous calcium lactate.

An examination of a large number of commercial and specially prepared samples showed that there are two kinds of calcium lactate. One is soluble in 20 parts of water at 23° and the other is soluble in 16 parts of water. Since different methods of manufacture give products of different solubility it is useless to set a single standard for solubility.—*N. Glass, Quart. J. Pharm.*, 1933, 522.

The solubility does *not* decrease on keeping nor is there any appreciable loss of water of crystallisation. The solubility varies with the method of preparation but does not appear to be due to any variation in constitution.—*G. H. Macmorran, Pharm. J.*, i/1933, 245.

Ferri Lactas (*B.P.C.* '34). $C_6H_{10}O_6Fe \cdot 3H_2O = 288.0$. Residue on ignition, 26.5% to 28.5% being equivalent approximately to a purity of 96%. Tartaric, citric and malic acids are tested for by addition of lead acetate solution. By titration with sodium thiosulphate of the iodine liberated on the addition of potassium iodide and hydrochloric acid, a ferric iron limit of about 0.8% is specified. The *N.F. V* salt, assayed for total iron content by oxidation with hydrogen peroxide and hydrochloric acid, evaporation and boiling with more acid, and finally digestion with potassium iodide for 30 minutes at 40° and titration with thiosulphate, contains not less than 97% of $Fe(C_3H_5O_3)_2 \cdot 3H_2O$.

ACIDI LACTICI BACILLI

Lactic Acid Bacilli Preparations. To arrest growth of putrefactive (alkaline) organisms in the intestines and hence stimulate intestinal digestion and diminish toxic absorption from the bowel, Prof. Elie Metchnikoff proposed the acclimatisation of the (harmless) lactic acid bacillus. Experimental consumption of large quantities of lactic bacilli showed that intestinal putrefaction was diminished.

It was found that with a normal diet the bacillus appeared in the stools in 3 to 4 days after it had been consumed regularly with the food; that it took 8 days to become properly acclimatised in the intestine, and that when this had taken place it would continue to live and thrive for 12 more days without another dose being swallowed, afterwards gradually disappearing. Regular administration caused increase in weight and bulk of fæces (*cf. work under B. Acidophilus, postea*).

Lactic acid, as such, has been employed for years past in dyspepsia, enteritis, etc., and locally in tuberculous ulceration of the larynx.

The conclusion was that as organisms of putrefaction only increase with difficulty in neutral or acid media, the most feasible procedure would be to introduce a lactic acid organism (growing in a sugar medium) into the human being to arrest the proliferation of harmful bacteria. The bacillus known as the Bulgarian Bacillus (*B. Caucasicum*), isolated by Cohendy and independently by Massol from "Yoghourth," a form of soured milk, was deemed most suitable as it is the best acid producer. The acid it produces is the optically inactive variety. It is a hardy organism resisting the stomach juices and its own acidity to a marked degree.

According to Hewlett it occurs apparently in various forms. In natural soured milks *B. Bulgaricus* and *B. Massol* from Bulgarian Yohourt and Maya, *B. Mazun* from Armenian mazun, *B. Lactis Acidi* (Leishman), etc., are probably varieties of only one species.

Buttermilk in many countries, **Kephir** or **Koumiss**, *vide* Vol. I, p. 583, the Egyptian "Leben Raib," "Prostokwocha," and "Varentez," of Russia, Yoghourth (Yohourt) of the Balkans, and many others, were forerunners of

the curdled milk treatment, which attracted so much attention. It is believed that the Bulgarian peasant consumes as much as 10 g. of lactic acid daily in his diet of Yohourt.

In Sardinia the people prepare and make a continuous diet (for lack of anything better) of Gioddu Mezzoraddu, or Miciaratu, which are the products of fermentation due to *Saccharomyces Sardons* and to *Bacillus Sardons* and *Mazun*. At Milan the grape ferment is in demand, at Turin Blastoinvertin (*Saccharomyces invertens*), in Lombardy Kephir, and at Piedmont the true Yohourt.

In Greece Yohourt is much in use both as a food and for treatment. It is prepared there by adding a little lemon-juice to fresh milk, which is kept warm for 8 hours, forming a curd. From the curd a tablespoonful is mixed with boiled milk, and this procedure is repeated several times, with fresh milk on each occasion, until a Yohourt of suitable consistency is obtained. Small spoonfuls of this latter product are added to wooden or earthenware pans containing milk which has been boiled and is still slightly warm. This forms the commercial Yohourt, which curdles in 4 hours at 35°. In order to keep it, and this one may do for as long as from 5 to 8 days, it is poured into little bags of cotton from which the whey filters, the products thereby becoming thicker and of better keeping qualities.

The Bulgarian Bacillus will produce as much as 2.5 g. of lactic acid per 100 ml. of milk.

Succinic, acetic and formic acids are also formed by it in small quantity. This bacillus has no action on albuminoids (casein, etc.) nor fats, nor does it produce alcohol or acetone. It does not attack saccharose (cane sugar) or maltose; it is therefore useless to add cane sugar in the hope of increasing lactic acid yield.

Gunther's Bacillus is found in abundance in all spontaneously coagulated milk and is an important lactic acid producer. It produces pure dextrorotatory lactic acid (no other acid) from grape and milk sugar.

Huppe's Bacillus is another lactic acid organism. It is almost always present in milk which has soured spontaneously. This organism, sometimes called specifically the *B. Acidi Lactici*, differs from *B. Guntheri* by its comparative ease of cultivation upon ordinary media.

The characters of the chief lactic acid organisms may be tabulated:—

Organism	Appearance	Properties
<i>Bacillus Caucasicum</i> (Kern); <i>Syn.</i> Massol's Bacillus, Bouchard's Bacillus, Bulgarian Bacillus.	Large square-shaped, 5 to 6 $\mu \times 1 \mu$ showing vacuoli, slightly motile. + Gram staining.	Takes time to establish but ultimately is the omnipresent bacterium in milk. A strong lactic acid producer.
Hüppe's Bacillus; <i>Syn.</i> <i>B. Acidi Lactici</i> . <i>Streptococcus Lebenis</i> may be closely allied.	Coccoid shape, 0.4 to 0.6 $\mu \times 0.6$ to 2 μ ; in pairs, rarely chains, non-motile. + Gram staining (opinions differ).	Causes bitterness, breaks up fat and proteolytic substances.
<i>Bacillus Guntheri</i> , <i>Syn.</i> <i>B. Acidi Paralactici</i> (Kozai).	Short rods, 1 $\mu \times 0.5$ to 0.6 μ , with pointed ends, in pairs or short chains, non-motile. — Gram staining.	Gives a smooth curd; appears to be ousted to some extent in curdling by <i>B. Caucasicum</i> .

Yohourt. Preparation—Raise the milk to boiling point. Remove from the heat and cool enough for a skin to form on top. While still too hot to be held conveniently inoculate by allowing some previous Yohourt—thinned with sterile water, if necessary—to slip down the edge of the container all round the rim. Cover, and, without shaking, place in a closely fitting hay-box until the next day. Do not allow to cool before placing in hay-box.

METHODS OF EXAMINATION OF LACTIC ACID BACILLI PREPARATIONS

Loopfuls of the milk, treated with a crushed lactic acid bacillus tablet (*vid.* Vol. I) are to be examined after 10 and 24 hours' cultivation.

Stain by "Gram," using 1% neutral red as counterstain. The gram-staining organisms are deep violet, the rest of the field reddish pink. A copious growth of *B. Caucasicum* is essential, with exclusion of other bacteria.

Curd formation should also be satisfactory. The property of producing lactic acid is common to a vast number of organisms.

Lactic acid content depends on the lactose content, the average of the latter being 4%. The decomposition of lactose in milk into lactic acid is a complex matter. Nature will not allow a theoretical yield, as the bacilli kill themselves by the acid they produce—the maximum acid formation being reached in about 36 hours. The *activity of the culture* is more important than the quantity of acid.

The maximum amount of acid is about 0·8% or more if longer time is allowed.

Milk, it should be noted, is amphoteric in reaction on account of its content of alkali phosphate. 20 ml. is a convenient quantity to titrate, using N/10 soda and phenolphthalein.

B. Acidophilus. In gram-stained smears from human fæces and from milk and whey-broth cultures, *B. acidophilus* appears as a rather long, stout, gram positive rod, characteristically curled towards the ends. Great variation occurs in length. Some varieties occur as short gram-positive bacilli, with a tendency to chain-formation, especially on isolation from rats' or dogs' fæces. In culture on whey-agar two types of colony of *B. acidophilus*, designated "X" and "Y," are frequently seen side by side. The former have a decidedly fuzzy appearance and are indistinguishable from *B. Bulgaricus*, while the latter is small, round or spindle-shaped, only partly fringed and at times almost perfectly smooth. The "X" colonies can be differentiated from *B. Bulgaricus* by the fact that *B. acidophilus* produces acid in 1% maltose broth after incubation at 37° for 48 hours while *B. Bulgaricus* does not. The implantation of *B. acidophilus* in the intestine is possible. *It was not found possible to implant B. Bulgaricus in the intestine by giving milk infected in the usual way. This may be due to the fact that unlike B. acidophilus, it is not a normal inhabitant of the human intestine.*—Ralph P. Smith, *Brit. med. J.*, ii/1924, 948.

A study of *B. acidophilus* in human fæces. The term "*B. acidophilus*" may cover a considerable group of organisms and numerous strains may exist even in one sample of food.—J. Cruickshank and D. W. Berry, *Brit. med. J.*, ii/1924, 944.

Of 8 commercial "Acidophilus" products only 5 stated on the label the number of viable organisms and of the 5 only 3 fulfilled their claims.—*J. Amer. med. Ass.*, ii/1928, 1192.

ACIDUM NITRICUM

Acidum Nitricum (*B.P.* '32). Contains 69% to 71% by weight of HNO_3 . Sp. gr., about 1·42. **Acidum Nitricum Dilutum** *B.P.C.* '34, contains 9·5% to 10·5% *w/w* of HNO_3 , with sp. gr. 1·054 to 1·060 and is of the same strength as the dilute acid of the *B.P.* '14. The acid of the *U.S.P. X* contains 67% to 69% of HNO_3 . **Acidum nitricum**, *P.G. VI*, contains 24·8% to 25·2% of HNO_3 , **Acidum nitricum crudum** 61% to 65% and **Acidum nitricum fumans** not less than 86%. **Acidum nitricum concentratum**, *P. Helv. V*, contains 64% to 66% *w/w* of HNO_3 .

Potassii Nitras (*B.P.* '32). $\text{KNO}_3 = 101·1$. A purity of 99% is required. The assay process of the *B.P.* reduces the nitrate with nascent hydrogen obtained by addition of sulphuric acid and reduced iron, liberating the ammonia formed with sodium hydroxide, distilling into excess of standard acid and back titrating with sodium hydroxide; a blank titration is performed. The *B.P.* '14 salt was not standardised. **Potassii Nitras**, *U.S.P. X*, contains 99% of KNO_3 after drying to constant weight at 100°; assayed by evaporation with hydrochloric acid and titration of the chloride with silver nitrate and potassium thiocyanate.

Sodii Nitris (*B.P.* '32). $\text{NaNO}_2 = 69.005$. Estimated by titration of standard potassium permanganate, acidified with sulphuric acid, diluted, and warmed to 40° , with a 0.5% solution of the salt. 95% purity is required. *Sodii Nitris, U.S.P. X*, contains 95% after drying over sulphuric acid. A solution of the salt is added to excess acidified permanganate, warmed to 40° , stood for 5 minutes and then back titrated with standard oxalic acid.

Spiritus Ætheris Nitrosi (*B.P.* '32). Contains from 1.25% to 2.5% *w/v* of ethyl nitrite, approximately the same as the *B.P.* '14 preparation which was required to contain 1.52% to 2.66% *w/w*. Sp. gr., 0.838 to 0.842. There is also a test for limit of acid. Assayed by the *B.P.* process in which the ethyl nitrite is decomposed by shaking in a brine-charged nitrometer with potassium iodide solution and dilute sulphuric acid, the liberated nitric oxide being measured. Each ml. of moist nitric oxide is equivalent to 0.0032 g. of $\text{C}_2\text{H}_5\text{O}_2\text{N}$. *Spiritus Ætheris nitrosi, P. Helv. V*, is a solution in absolute alcohol containing from 2% to 2.5% *w/v* of ethyl nitrite. It is assayed as follows:—Shake vigorously for 5 minutes in a closed flask 20 ml. of N/10 silver nitrate, 10 ml. of the spirit, 20 ml. of saturated solution of potassium chlorate and 5 ml. of dilute nitric acid, and then dilute to 100 ml. with water. Filter and titrate 50 ml. of the filtrate with N/10 ammonium thiocyanate using iron alum as indicator; each ml. of N/10 AgNO_3 used up is equivalent to 0.022515 g. of $\text{C}_2\text{H}_5\text{O}_2\text{N}$.

This preparation decomposes even when kept under the best conditions. The first change is probably the formation of aldehyde and nitrous acid, and then the aldehyde is oxidised into acetic acid. In the course of time the nitrous constituent of the spirit entirely disappears, but aldehyde, one of the most readily oxidisable bodies, remains. The spirit should be kept in cool cupboards and in well-filled bottles, preferably upside down.

With regard to the volatilisation of ethyl nitrite, Cowley has shown that every trace of ethyl nitrite disappears from a solution within a few days in ordinary vessels. As to decomposition in an aqueous solution, a mixture containing spirit of nitre loses the whole of it in three days. Solutions in absolute alcohol change less rapidly than those in 90% alcohol on account of the water present. A mixture of 90% alcohol and glycerin in equal volumes is a good solvent for all preparations of ethyl nitrite.

Uranii Nitras (*B.P.C.* '34). $\text{UO}_2(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O} = 502.2$. Determined gravimetrically by precipitation as hydroxide and ignition to oxide, U_3O_8 . A limit of uranous compounds, as shown by the decolourisation of potassium permanganate, is specified. Limit tests for alkaline earths, lead, iron, manganese and zinc are included and it should contain 98% of the pure substance.

ACIDUM OLEICUM

Acidum Oleicum (*B.P.* '32). Consists chiefly of $\text{C}_{17}\text{H}_{33}\text{COOH}$. Sp. gr., about 0.898. Acid value, 195 to 200. Iodine value, 85 to 90. It should not become cloudy on cooling until a temperature of 10° has been reached; a higher point indicates the presence of stearic acid; it congeals at about 4° . Should comply with limits for mineral acids and for neutral fats and mineral oils. Ash not more than 0.1% *w/w*. The *U.S.P. X* substance is not required to comply with stated acid value or iodine number.

Acidum Stearicum (*B.P.C.* '34). Should not melt below 54° . Acid value, 200 to 210. Complies with a limit test for neutral fat or paraffin. *Acidum Stearicum, U.S.P. X*, should not melt below 56° and has a congealing point not below 54° .

Alcohol cetylicus, *P. Helv. V*, $\text{C}_{16}\text{H}_{33}\text{OH}$, melts between 48° and 50° and contains no saponifiable matter. LANETTE WAX is a commercial form of this alcohol.

ACIDUM PHOSPHORICUM

Acidum Phosphoricum (*B.P.* '32). Contains 88% to 90% *w/w* of H_3PO_4 with a sp. gr. of about 1.75. The corresponding

acid of the 1914 Pharmacopœia contained only 66·3% with sp. gr. 1·5. No brown colour, indicative of phosphorous and hypophosphorous acids, is produced on warming with silver nitrate. Acidum Phosphoricum Dilutum, *B.P.* '32, contains 9·5% to 10·5% *w/w* of H_3PO_4 . Assayed in saturated salt solution by titration with N/1 sodium hydroxide, using phenolphthalein as indicator; each millilitre of normal solution is equivalent to 0·04902 g. of H_3PO_4 . The corresponding acids of the *U.S.P. X* contain 85% to 88% and 9·5% to 10·5% of H_3PO_4 respectively. Assayed by neutralisation to phenolphthalein with chloride-free sodium hydroxide, addition of excess N/10 silver nitrate and adjustment to neutrality to litmus with zinc oxide, followed by dilution to known volume, filtration and titration of an aliquot part of the filtrate with potassium thiocyanate using ferric ammonium sulphate as indicator; each millilitre of N/10 solution is equivalent to 0·003269 g. of H_3PO_4 . Acidum phosphoricum, *P.G. VI*, contains 24·8% to 25·2% of H_3PO_4 .

The best method for the complete titration of P_2O_5 , NaH_2PO_4 and Na_2HPO_4 is the use of phenolphthalein at a temperature of 55° to 70° after CaCl_2 has been added to the phosphate solution. The proportion of phosphate to CaCl_2 should be 1 in 2 to 1 in 5.—per *Yearb. Pharm.*, 1926, 305.

Metaphosphoric Acid, $\text{HPO}_3 = 80·035$, is equivalent to *glacial phosphoric acid*, and is employed as an albumin test (*vide Urine*).

Ammonii Phosphas (*B.P.C.* '34). A mixture of the di-ammonium and di-hydrogen salts, containing not less than 20% of NH_3 . The *B.P.C.* directs 1 g. to be dissolved in 200 ml. of water, 25 ml. of 25% sodium hydroxide solution added, the liberated ammonia distilled into 50 ml. of N/2 sulphuric acid and the excess acid titrated with N/2 sodium hydroxide to methyl red. Ammonii Phosphas, *N.F. V*, contains the two compounds equivalent to not less than 22% of combined ammonia.

Calcii Phosphas (*B.P.* '32). Assayed by addition of ammonium acetate and ammonium oxalate to a solution slightly acidified with hydrochloric acid, heating and allowing to stand for several hours, filtration and ignition with sulphuric acid of the washed precipitate. Contains calcium equivalent to 85% of $\text{Ca}_3(\text{PO}_4)_2$. Calcii Phosphas Præcipitatus, *N.F. V*, loses not more than 4% of moisture at 200°; no assay is included. Calcium phosphoricum bibasicum, *P. Helv. V*, is determined by dissolving 1 g. in 25 ml. of N/1 hydrochloric acid, diluting with 150 ml. of water and titrating to methyl orange with N/1 sodium hydroxide; 1 ml. is equivalent to 0·1361 g. of CaHPO_4 and the salt should contain from 78·8% to 80·2% of anhydrous CaHPO_4 . Mono- and tribasic salts are excluded by titration to phenolphthalein after the previously neutralised solution has been treated with neutral calcium chloride solution. The same salt for veterinary use must contain from 35% to 38% of P_2O_5 . Calcium phosphoricum monobasicum, *P. Helv. V*, contains by the methods prescribed not more than 5% of free phosphoric acid and not less than 92% of $\text{Ca}(\text{H}_2\text{PO}_4)_2 + \text{H}_2\text{O}$. Calcium phosphoricum tribasicum, *P. Helv. V*, is assayed by dissolving about 1 g., accurately weighed, in 25 ml. of N/1 hydrochloric acid, diluting with 200 ml. of water and, after adding 3 or 4 drops of methyl orange, titrating with N/1 sodium hydroxide until the red colour disappears, rotating constantly to redissolve the precipitate formed. Each ml. of N/1 HCl is equivalent to 0·07756 g. of $\text{Ca}_3(\text{PO}_4)_2$ and the salt should contain not less than 95%.

Magnesii Phosphas (*B.P.C.* '34). Consists of $\text{Mg}_3(\text{PO}_4)_2$ with about 30% of combined water. The residue on ignition ($\text{Mg}_2\text{P}_2\text{O}_7$) corresponds to not less than 68% of $\text{Mg}_3(\text{PO}_4)_2$.

Potassii Phosphas (*B.P.C.* '34). $\text{K}_2\text{HPO}_4 = 174·2$. Loses not more than 5% at 100° and then contains 98% of the pure substance. Assayed by titration with N/2 sulphuric acid to the green colour of bromocresol green indicative of pH 4·5, which converts the dipotassium compound into the di-hydrogen compound.

Potassii Phosphas Acidus (*B.P.C.* '34). $\text{KH}_2\text{PO}_4 = 136·1$. Contains 97% of KH_2PO_4 . Titrated with standard sodium hydroxide in the presence of sodium chloride using phenolphthalein as indicator. A limit of dipotassium phosphate

neutralisation with N/10 sulphuric acid to the pH 4·5 green colour of bromocresol green, equivalent to about 1·7% of K_2HPO_4 , is included.

Sodii Phosphas (*B.P.* '32). $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O} = 358\cdot2$. Assayed by titration pH 4·5 with N/2 sulphuric acid, using bromocresol green as indicator replacing the *B.P.* '14 titration to H_3PO_4 with methyl orange indicator. Contains from 99·5% to the equivalent of 105% of $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$. *Sodii Phosphas, U.S.P. X*, containing 39·25% to 44·00% of Na_2HPO_4 corresponding to not less than 99% of $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$, is assayed by the method for phosphates—addition of excess silver nitrate, neutralisation with zinc oxide, filtration, and titration of an aliquot part with potassium thiocyanate.

Sodium phosphate may contain fluoride as impurity, which may cause serious disturbance in biochemical work.—A. Harden, *Nature*, ii/1934, 101.

The addition of 10 ml. of a 33% solution of sodium hexametaphosphate (Calgon) to the Fehling's solution immediately before the addition of the invert sugar will eliminate interference due to the presence of calcium. When an excess of sodium hexametaphosphate is added to a solution of a calcium salt the calcium becomes inert and cannot be detected by any of the normal reagents.—J. G. W. Maskin, *Analyst*, 1935, 318.

Sodii Phosphas Acidus (*B.P.* '32). $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O} = 156\cdot1$. Contains not less than 98% of the pure salt. The addition of 25% of sodium chloride to the solution for titration replaces the use of glycerin, as in the 1914 Pharmacopœia, and the assay with half normal sodium hydroxide using phenolphthalein as indicator. A titration of not more than 1 ml. of N/10 sulphuric acid for 1 g. of salt, to bromocresol green, represents a limit of the di-sodium salt equivalent to about 1·4% of Na_2HPO_4 . The *U.S.P. X* requires *Sodii Biphosphas* to lose not more than 15% of water when dried for 1 hour at 60° and then at 100°; it then contains 98% of the anhydrous acid phosphate; the silver nitrate assay of a neutralised solution, completed as for the disodium compound, is included in addition to the titration with sodium hydroxide to phenolphthalein in presence of sodium chloride.

Sodii Phosphas Exsiccatus (*B.P.C.* '34). Loses not more than 2% at 100° and then contains 99% of Na_2HPO_4 , determined by the *B.P.* method for *Sodii Phosphas*. *Sodii Phosphas Exsiccatus, U.S.P. X*, contains 98% of the anhydrous compound after drying to constant weight at 110°; no limit of moisture is specified. It is assayed by the silver nitrate process for *Sodii Phosphas, U.S.P. X*.

Sodium Acid Pyrophosphate, as used in baking powder, is the anhydrous compound, $\text{Na}_2\text{H}_2\text{P}_2\text{O}_7$. The aqueous solution is neutral to methyl orange and acid to phenolphthalein.

ACIDUM SALICYLICUM

Acidum Salicylicum (*B.P.* '32). $\text{C}_6\text{H}_4\text{OH} \cdot \text{COOH} = 138\cdot0$. M.p., 158° to 159°. When titrated in alcoholic solution with N/2 sodium hydroxide using phenol red as indicator a purity of 99·5% is indicated. Ash not more than 0·05%. No assay was included in the 1914 Pharmacopœia. The *U.S.P. X* requires the same purity after drying the acid for two hours at 100°; titration is made with N/10 barium hydroxide using phenolphthalein as indicator. *Acidum salicylicum, P. Helv. V*, is required to contain at least 99·6% of the pure acid and to melt between 155° and 157°.

Self's Vanadate Test for Salicylic Acid. Mix equal parts by volume of 10% formaldehyde and conc. sulphuric acid and cool the mixture thoroughly. Moisten the substance to be tested in a dish with the mixture, add a little ammonium vanadate and stir well. If salicylic acid is present a prussian blue colour appears immediately changing rapidly to greenish blue and finally green. For about 1 mg. of salicylic acid use 2 drops of the liquid and 2 to 3 mg. of ammonium vanadate. The only other substance giving the colour is salicylic aldehyde.—*Pharm. J.*, i/1915, 521.

3 : 5-Dibromsalicylic Acid is considerably more active than salicylic acid as a bactericide.—*Yearb. Pharm.*, 1927, 227.

Use as Preservative (not now allowed) see *Food Preservative Regns.*

It has the disadvantage of sometimes giving the odour of phenol. Its use

where otherwise rapid decomposition would occur has been upheld by some in the past, e.g., 1 grain per pint or 1 grain per lb.

Detection. Concentrate liquid (distil off any alcohol) in presence of alkali and sodium chloride, acidify and shake out with chloroform, evaporate and add ferric chloride solution—violet colour. *See also* Scheme for Recognition of Organic Chemicals.

Lithii Salicylas (*B.P.C.* '34). $C_7H_5O_3Li = 144.0$. Dried at 120° it contains not less than 98.5% of $C_7H_5O_3Li$. Loses not more than 3% of its weight at 120° . Assayed by the *B.P.* method for Sodii Salicylas: about 3 g. dissolved in 50 ml. of water, with 50 ml. of ether and a little bromophenol blue indicator are shaken and titrated with N/2 sulphuric acid until a colour change takes place; the titration of the separated aqueous layer, a 10 ml. water washing of the ethereal layer and a fresh 20 ml. of ether is completed, with constant shaking. Lithii Salicylas, *N.F. V*, dried to constant weight at 120° , contains not less than 98.5% of $LiC_7H_5O_3$. The *N.F. V* assay process is directed to be performed on the substance dried for 24 hours over sulphuric acid, igniting with twice its weight of ammonium sulphate, and weighing as Li_2SO_4 .

Magnesii Salicylas (*B.P.C.* '34). $C_{14}H_{10}O_6Mg \cdot 4H_2O$. Loses not more than 19% at 110° and then contains 99% of the anhydrous salt. Assayed by the *B.P.* process for Sodii Salicylas by titration with standard sulphuric acid to bromophenol blue.

Potassii Salicylas (*B.P.C.* '34). $C_7H_5O_3K = 176.1$. Dried at 110° it contains 99% of the pure substance. Moisture, determined at 110° , not more than 1%. Assayed by the *B.P.* ether-acid titration used for Sodii Salicylas.

Sodii Salicylas (*B.P.* '32). $C_6H_4OH \cdot COONa = 160.0$. A purity of 99.5% is required for the substance dried at 110° . Loss at 110° not more than 1%. The separated salicylic acid melts between 158° and 159° . The assay of the *B.P.* '11 by titration with standard acid of the alkaline residue on ignition, is replaced by titration with half normal sulphuric acid, removing the liberated acid with ether and using bromophenol blue as indicator. Sodii Salicylas, *U.S.P. X*, after drying to constant weight at 100° , contains 99.5% of $NaC_7H_5O_3$. No limit of moisture is specified; assayed by dissolving the carbonised residue in excess acid and back titrating with standard alkali to methyl orange.

Discolouration of Solutions. Solutions with sodium bicarbonate become dark due to oxidation. A small quantity of sodium sulphite, pyrosulphite or thiosulphate prevents discolouration.—H. G. Greenish and A. E. Beesley, *Pharm. J.*, i/1915, 201.

Methylis Salicylas (*B.P.* '32). $C_8H_8O_3 = 152.1$. Assayed by the *B.P.* process for esters in volatile oils by saponification of the neutralised substance with N/2 alcoholic potash during one hour, dilution, and back titration with standard sulphuric acid to phenolphthalein. A blank titration on the alcoholic potash is performed; each millilitre of N/2 alcoholic potash is equivalent to 0.07603 g. of $C_8H_8O_3$; a titration difference indicating not less than 98% should be obtained. Sp. gr., 1.186 to 1.191; refractive index at 20° , 1.536 to 1.583. Methylis Salicylas, *U.S.P. X*, may be the synthetic or the natural substance and must be labelled accordingly. In assaying, the saponification is allowed to proceed for 2 hours; a purity of 98% is required.

Oleum Betulæ (*B.P.C.* '34). This naturally occurring oil should contain 98% w/w of esters calculated as methyl salicylate and determined by the *B.P.* ester process. Sp. gr., 1.182 to 1.192; optical rotation, $+0.5^\circ$ to -0.5° ; refractive index at 20° , 1.534 to 1.538.

Distinction from Methyl Salicylate. To 5 drops of the oil in a test tube add 5 drops of a 5% alcoholic solution of vanillin and 1 ml. of alcohol, shake well and add 2 ml. of concentrated sulphuric acid; mix thoroughly. Sweet birch oil gives a red colouration while methyl salicylate gives a yellow.—*Perfum. essen. Oil Rec.*, 1914, 60.

Salol (*B.P.C.* '34). $C_6H_4 \cdot OH \cdot COOC_6H_5$. The *B.P.C.* requires the substance to melt between 42° and 43.5° . Phenylis Salicylas, *U.S.P. X*, melts between 41° and 43° .

ACIDUM SULPHURICUM

Acidum Sulphuricum (*B.P.* '32). Contains not less than 95% w/w of H_2SO_4 with a sp. gr. of about 1.84. The *B.P.* limits the amount of oxidisable impurities present by addition of

0.1 ml. of N/10 potassium permanganate to a cooled mixture of 5 ml. with 20 ml. of water, which should not be decolorised within 5 minutes; and nitrate by 5 ml. with 5 ml. of water not decolorising 0.5 ml. of indigo carmine solution. Acidum Sulphuricum Dilutum, *B.P.*, contains from 9.5% to 10.5% *w/w* of H_2SO_4 , and has a sp. gr. of 1.064 to 1.073. The strong acid of the *U.S.P.* *X* contains from 93% to 95% of H_2SO_4 ; sp. gr., about 1.83 at 25°; the dilute acid is of the same strength as the corresponding *B.P.* acid. Acidum sulfuricum, *P.G. VI*, contains 94% to 98%, Acidum sulfuricum crudum not less than 94%, and Acidum sulfuricum dilutum from 15.6% to 16.3% of H_2SO_4 .

Sulphuric acid is used in manufacture of glucose which is employed in making beer. Owing to it being made from pyrites, it contaminated the glucose and thence the beer with arsenic in 1900. *Vide* also Arsenum.

Sulphur in Coal Gas. Prior to 1906 parliamentary restriction prevented the presence of more than 20 grains of sulphur per 100 cubic feet, but this restriction was removed and regarded as unnecessary. The sulphur contained in the gas supplied to the public contains only 3% of the sulphur present in the original coal, so that the substitution of gas for coal must necessarily diminish to a negligible quantity the pollution of the air with sulphurous gases.

The following figures for sulphur contained in the gas of the three principal London gas companies are given in the Annual Report of the L.C.C. for the year 1927.

Company	Sulphur in grains per 100 cu. ft. of gas
Gas Light and Coke Co.	26.1
South Metropolitan Gas Co.	20.0
Commercial Gas Co.	27.5

Calcii Sulphas Exsiccatus (*B.P.C.* '34). $\text{CaSO}_4, \frac{1}{2}\text{H}_2\text{O} = 145.1$. The *B.P.C.* specifies the solidifying power; a mixture of 20 g. with 10 ml. of water at 15° to 20° sets in about three minutes, the test being performed in a cylindrical container of about one inch diameter; after 3 hours the edges of the moulded mass retain their sharpness of outline and do not crumble under pressure of the fingers.

Ligamentum Calcii Sulphatis (*B.P.C.* '34). The weight of a length of 4 yards of 2-inch bandage is not less than 2.5 ounces, the fabric alone weighing not less than 85 grains; other widths should be in proportion; not less than an average of 33 threads in the warp and 19 in the weft, per inch. The bandage should be reasonably free from loose powder and 75% of the weight of the bandage should be plaster of paris which is adherent to the fabric.

Cupri Sulphas (*B.P.* '32). $\text{CuSO}_4, 5\text{H}_2\text{O} = 249.7$. Estimated by interaction of the cupric salt with potassium iodide in solution containing 10% of acetic acid, the liberated iodine being titrated with standard thiosulphate solution, using starch mucilage as indicator. Should contain from 98.5% to the equivalent of 101% of $\text{CuSO}_4, 5\text{H}_2\text{O}$. No standard or method of assay was included in the *B.P.* '14. Cupri Sulphas, *U.S.P. X*, contains from 63% to 66.8% of anhydrous compound, equivalent to not less than 98.5% of the crystallised substance.

Insecticides. The specification of the Association of British Insecticide Manufacturers (Bulletin No. 82: Ministry of Agriculture and Fisheries) requires: COPPER SULPHATE to contain not less than 98% crystallised copper sulphate ($\text{CuSO}_4, 5\text{H}_2\text{O}$);

BORDEAUX POWDER to contain no water-soluble copper, and the equivalent amount of copper to be declared;

CHESHUNT COMPOUND to consist of 2 parts of copper sulphate and 11 of ammonium carbonate by weight, and to contain not less than the equivalent of 3.8% Cu;

BURGUNDY POWDER to contain not more than 2% alkalinity expressed as Na_2CO_3 and no water-soluble copper, the whole of the powder to pass through a 30-mesh B.S. sieve.

Magnesii Sulphas (*B.P.* '32). $\text{MgSO}_4, 7\text{H}_2\text{O} = 246.5$. The 97.4% standard of the 1914 Pharmacopœia is replaced by a standard of not less than 99.5% and not more than the equivalent of 102% of the pure salt. Assayed by precipitation

as magnesium ammonium phosphate with sodium phosphate in ammoniacal solution containing ammonium chloride, filtration after shaking and standing, washing with 2% ammonia solution and final ignition to pyrophosphate. The substance of the *U.S.P. X* is required to contain from 48.60% to 53.45% of MgSO_4 , corresponding to not less than 99.5% of the heptahydrate.

Magnesii Sulphas Exsiccatus (*B.P.C.* '34). Contains from 62% to 70% of MgSO_4 , when precipitated as the magnesium ammonium phosphate compound and ignited to pyrophosphate. Magnesium sulfuricum siccum, *P. Helv. V* contains about two molecules of water and on heating to a low red heat loses from 22.5% to 25% of water.

Ammonii Persulphas (*B.P.C.* '34). $(\text{NH}_4)_2\text{S}_2\text{O}_8 = 228.2$. Contains not less than 98% of the pure substance. Assayed by the method of the *B.P.C.* '34: to 0.5 g. dissolved in 10 ml. of water, 50 ml. of $\text{N}/10$ oxalic acid and 0.2 g. of silver sulphate in 20 ml. of dilute sulphuric acid are added, after heating on a water-bath till evolution of carbon dioxide has ceased the mixture is diluted and the excess oxalic acid titrated with standard potassium permanganate.

Potassii Persulphas (*B.P.C.* '34). $\text{K}_2\text{S}_2\text{O}_8 = 270.3$. Assayed by the oxidising action of one equivalent of oxygen upon excess oxalic acid, as in the *B.P.C.* titration for Ammonii Persulphas, it contains not less than 98% of $\text{K}_2\text{S}_2\text{O}_8$.

Sodium, Ammonium and Potassium Persulphates are strong bleaching agents, the last known as Anthion, and the ammonium salts are used in photography to reduce dense negatives—they oxidise and then dissolve part of the silver. On adding barium chloride to a solution of a persulphate there is no precipitation, but on warming, barium sulphate is thrown down.

The ammonium salt is prepared by electrolysis of a solution of ammonium sulphate containing sulphuric acid. In presence of water it yields ozonized oxygen. It bleaches, and has been used as a hand disinfectant and to sterilise sponges.

For details of the therapeutic use of the sodium salt, see Vol. I, p. 771.

Potassii Sulphas (*B.P.C.* '34). $\text{K}_2\text{SO}_4 = 174.3$. Contains not less than 99% of the pure salt, determined gravimetrically by precipitation and ignition of the barium compound. A 2% solution should not be acid to methyl orange. Potassii Sulphas, *N.F. V*, contains 99% after drying to constant weight at 100° .

Sodii Sulphas (*B.P.* '32). $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O} = 322.2$. Assayed by weight of the ignited barium salt, it contains not less than 99% and not more than the equivalent of 102% of $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$. The substance of the *U.S.P. X* contains from 43.64% to 48% of Na_2SO_4 , corresponding to not less than 99% of the decahydrate.

Sodii Sulphas Exsiccatus (*B.P.C.* '34). $\text{Na}_2\text{SO}_4 = 142.1$. Loses not more than 5% of its weight at 100° , and then contains not less than 99% of the anhydrous substance. Assayed by precipitation with barium chloride and ignition of the insoluble sulphate. Natrium sulfuricum siccum, *P.G. VI*, contains not less than 88.6% of Na_2SO_4 .

Zinci Sulphas (*B.P.* '32). $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O} = 287.5$. Assayed by the process of the British Pharmacopœia: a solution of 0.4 g. in 120 ml. of water, just acidified with dilute sulphuric acid and mercuric ammonium thiocyanate solution added, is set aside to crystallise; the filtered precipitate is washed with five 10 ml. quantities of diluted ammonium mercuric thiocyanate (1 : 50), and then titrated, after the addition of 40 ml. of hydrochloric acid and 5 ml. of chloroform, with $\text{M}/5$ potassium iodate. It contains from 99.5% to the equivalent of 101% of $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$. Zinci Sulphas, *U.S.P. X*, contains from 55.86% to 58.63% of ZnSO_4 , corresponding to not less than 99.5% of crystalline substance and is assayed by precipitation of the sulphide, evaporation in nitric acid solution and ignition to oxide.

In order to obtain accurate results with the *B.P.* assay process the titration with potassium iodate must be conducted *immediately* after adding the hydrochloric acid to the precipitate.

Barii Sulphas (*B.P.* '32). $\text{BaSO}_4 = 233.4$. Loss at 110° , not more than 2%. Soluble barium compounds and sulphide, sulphite and thiosulphate are among the impurities tested for. The substance of the *U.S.P. X* is described as barium sulphate freed from soluble barium salts. A test for "bulkiness of powder" is to be included in the revised *U.S.P.*; the substance in No. 60 powder is to be agitated with water in a measuring cylinder, the amount of powder settled after a stated time being measured.

ACIDUM SULPHUROSUM

Acidum Sulphurosum (*B.P.C.* '34). Contains not less than 4.5% and not more than 5.5% *w/w* of SO_2 , corresponding to 5.76% to 7.05% *w/w* of H_2SO_3 . Sp. gr. about 1.025. Estimated by oxidation with excess standard iodine and titration with sodium thiosulphate.

Sulphurous acid is a strong reducing agent. For example, many colours are bleached by the sulphurous acid combining with the oxygen of any water present, hydrogen being liberated, which latter forms colourless compounds with the colours. These compounds may then be removed by washing.

The gas compressed in small cylinders was used for room disinfection, but formaldehyde (*q.v.*) is more frequently used now.

"Clayton Gas," consisting principally of the residual nitrogen of the air, sulphurous acid up to 15%, and a considerable amount of sulphuric acid (which is useful, as it renders the gas visibly opaque), has been employed for freeing ships' holds from vermin. A special apparatus is used.

Sodii Sulphis (*B.P.C.* '34). $\text{Na}_2\text{SO}_3 \cdot 7\text{H}_2\text{O} = 252.2$. Assayed by addition of excess standard iodine solution and titration with sodium thiosulphate, using starch mucilage indicator, a purity of not less than 94% should be indicated. Thiosulphate is limited by absence of turbidity on addition of hydrochloric acid to a 10% aqueous solution.

Sodii Thiosulphas (*B.P.C.* '34). $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O} = 248.2$. On titration with N/10 iodine, not less than 99% of $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ is indicated. Sodii Thiosulphas, *U.S.P. X*, contains from 63.07% to 67.48% of $\text{Na}_2\text{S}_2\text{O}_3$, equivalent to not less than 99% of crystalline salt. Natrium thiosulfuricum is official in the *P.G. VI*.

Aurii et Sodii Thiosulphas (*B.P.C.* '34). $\text{Na}_3\text{Au}(\text{S}_2\text{O}_3)_2 \cdot 2\text{H}_2\text{O} = 526.5$. Should retain its colour, physical properties and solubility when kept in closed phials at 75° for 24 hours. Assayed by the *B.P.C.* process for Au content by treatment of 0.8 g. in 50 ml. of water with 10 ml. of N/1 sodium hydroxide and 10 ml. of 20 vols. hydrogen peroxide, boiling off excess peroxide and acidifying with hydrochloric acid; the coagulated precipitate of gold is washed, dried, ignited and weighed. A gold content of 37.0% to 37.6% is required.

ACIDUM TANNICUM

Acidum Tannicum (*B.P.* '32). Obtained from the galls of various species of *Quercus*, it loses from 6% to 12% of its weight at 100°. Gums, dextrin, sugar and salts are limited by the addition of an equal volume of alcohol to a 20% aqueous solution, and no turbidity is shown on the addition of a half volume of ether. The *U.S.P. X* acid should lose not more than 12% of its weight at 100°.

The identification by chemical methods of drugs containing tannins.—A. H. Ware, *Pharm. J.*, ii/1925, 131.

A review of the tannins in astringent drugs.—A. H. Ware, *Pharm. J.*, ii/1926, 162.

Commercial examination of tannins by comparative methods.—W. B. Forbes, per *Yearb. Pharm.*, 1926, 293.

Ammonium molybdate, 10% solution, gives a reddish-brown colour with tannic acid, also gallic acid, pyrogallol and tincture of catechu. May be used for colorimetric assay for tannin and drugs containing it.—J. Rae, *Pharm. J.*, i/1928, 539.

For a general account of the history, chemistry and distribution of the natural organic tannins see *The Natural Organic Tannins* by M. Nierenstein (J. & A. Churchill).

Acetannin (*B.P.C.* '34). Loses not more than 3% of its weight at 100°. A limit of the colour produced on adding ferrous tartrate solution to water shaken with the substance is specified and is equivalent to a tannic acid limit of 0.2%.

Acidum Gallicum (*B.P.C.* '34). $\text{C}_7\text{H}_5\text{O}_5 \cdot \text{H}_2\text{O} = 188.1$. Loss at 100°, not

more than 10%. A 5% solution should not be more than faintly yellow and does not precipitate with gelatin or albumen solutions.

Catechu (*B.P.* '32). The substance dried at 100° yields not more than 25% of water-insoluble matter. Loss at 100°, not more than 10%. Alcohol-insoluble matter dried at 100° and containing not more than occasional starch grains, not more than 30%. Ash, not more than 8%. Gambir, *U.S.P. X*, yields not less than 70% of water-soluble extractive and not less than 60% of alcohol-soluble extractive.

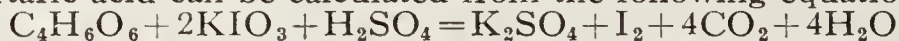
Catechu Nigrum (*B.P.C.* '34). Alcohol extractive, not less than 60%. Ash, not more than 8%.

ACIDUM TARTARICUM

Acidum Tartaricum (*B.P.* '32). $C_4H_6O_6 = 150.0$. Loses not more than 1% at 100° and then contains 99.5% of the pure substance. Acidum Tartaricum, *U.S.P. X*, contains 99.5% of $C_2H_2(OH)_2(COOH)_2$.

Detection in Syrups and Lemonades. Dilute 100 ml. of the liquid with 20 ml. of water and filter into a 300 ml. test-glass. Add 20 ml. of strong solution of calcium acetate, made by dissolving $CaCO_3$ 32 g. in glacial acetic acid 120 ml. and diluting to 1 litre with distilled water. Mix, stir well, and set aside for 72 hours. In presence of tartaric acid an evident crystalline deposit will be seen which is identified by micro-examination. Confirm by applying Denigé's Test (resorcin and sulphuric acid).—per *Yearb. Pharm.*, 1926, 179.

Determination of Tartaric Acid. About 0.3 g. of the acid is added to a flask containing 1 g. of potassium iodate, a few drops of water and 30 ml. of concentrated sulphuric acid, and the mixture is heated for about 30 minutes until most of the iodine is expelled. Water is added and the last traces of iodine are removed by boiling. By estimation of the remaining potassium iodate (by adding potassium iodide to an aliquot portion and titrating with thiosulphate) the amount of tartaric acid can be calculated from the following equation:—



—*J. chem. Soc. Abstr.*, ii/1924, 73.

An official quantitative method for the determination of tartaric acid in baking powders is described in *Methods of Analysis (A.O.A.C., 1930, 121)*.

Potassii Tartras (*B.P.C.* '34). $C_8H_8O_{12}K_4 \cdot H_2O = 470.5$. Contains not less than 99% of $C_8H_8O_{12}K_4 \cdot H_2O$. Assayed by titration of the alkaline residue on gentle ignition, with standard sulphuric acid to methyl orange.

Potassii Tartras Acidus (*B.P.* '32). $C_4H_5O_6K = 188.1$. The substance dried at 100° contains not less than 99.5% of the pure compound. Loss at 100°, not more than 1%. Assayed by titration of the boiling solution with N/5 sodium hydroxide to phenolphthalein. Potassii Bitartras, *U.S.P. X*, contains 99.5% of $KHC_4H_4O_6$ after drying at 100°.

Cream of Tartar Substitutes. These are usually calcium acid phosphate. A sample examined by Evans was a mixture of cream of tartar with sodium acid sulphate, but in such proportion that the whole of the tartaric acid would be liberated with the cream of tartar in solution, with an excess of about 10% $NaHSO_4$ still remaining. Another sample was a mixture of "dry" calcium acid phosphate and sodium chloride.

Sodium acid pyrophosphate, $Na_2H_2P_2O_7$, is also used as the acidic constituent of baking powders in place of tartaric acid and cream of tartar.

Sodii et Potassii Tartras (*B.P.* '32). $C_4H_4O_6NaK \cdot 4H_2O = 282.2$. By titration with standard sulphuric acid of the carbonised alkaline residue, using methyl orange as indicator, a purity of not less than 99% and not more than the equivalent of 104% should be found. Potassii et Sodii Tartras, *U.S.P. X*, contains from 73.72% to 77.39% of the anhydrous substance, corresponding to not less than 99% of the crystallised salt.

ACONITINA

Aconitina (*B.P.C.* '34). $C_{34}H_{47}O_{11}N = 645.4$. M.p. when heated rapidly, 196° to 200°, acetic acid being evolved. The

amount of pseudaconitine present is limited: 10 mg. dissolved in and evaporated with 5 drops of fuming nitric acid produces a yellow residue which should show no red colour on moistening with N/2 alcoholic potassium hydroxide. Aconitina, *U.S.P. X*, dissolved in water with a little acetic acid and injected under the skin of the abdomen of guinea pigs, has a minimum lethal dose of from 0.000000055 g. to 0.000000065 g. for each gramme of body weight of guinea pig, two-thirds of the number of guinea pigs being tested dying within 6 hours.

Aconitinum, *P. Helv. V*, contains not less than 99.1% of $C_{34}H_{47}O_{11}N$ and is determined by titrating a solution in a known excess of N/10 hydrochloric acid with N/10 sodium hydroxide using methyl orange.

Aconitine gives a reddish-violet colour when warmed with resorcinol and sulphuric acid, and the liquid becomes colourless with a blue fluorescence when made alkaline with strong sodium carbonate solution; a residue of total alkaloids of aconite gives the same reddish-violet colour, but when made alkaline a deep purple colour is produced with a green fluorescence.—C. Brugeas, *Ann. Falsif.*, 1932, 25, 147.

Pseudaconitine. A crystalline alkaloid obtained from Indian (or Nepaul) aconite, *A. laciniatum*, melts at 201° and has the constitution of acetyl-veratroyl-pseudaconine.

Most of the Japanese aconite plants contain several isomers and closely related aconitines. Methods of extraction and isolation of 6 isomers.—*Yearb. Pharm.*, 1925, 48, 49.

Aconitum (*B.P. '32*). The dried root of *Aconitum Napellus*; should not contain more than 2% of other organic matter. The Pharmacopœia states that there is no trustworthy chemical method of assaying the root, and does not consider the drug sufficiently important medicinally to include a biological method. Aconitum, *U.S.P. X*, contains not more than 5% of its stems and not more than 2% of other foreign organic matter; in the form of the tincture prepared by the official method for Tinctura Aconiti, *U.S.P. X*, it has a minimum lethal dose not exceeding 0.0004 ml. of tincture for each gramme body weight of guinea pig when administered subcutaneously. Pulvis Aconiti I.A. is adjusted, by dilution with rice starch if necessary, to contain 0.5% of total alkaloids.

Aconiti Radix of the 1914 Pharmacopœia was assayed for ether-soluble alkaloids of which it was required to contain not less than 0.40%. A tincture was prepared from 10 g. by maceration and percolation with 75% alcohol, and was then evaporated to dryness at a temperature not above 60° ; a filtered solution of the residue dissolved in 5 ml. of N/10 sulphuric acid and 20 ml. of water and washings was made ammoniacal with 2 ml. of solution of ammonia and shaken for one minute with 25 ml. of ether; after evaporation the aqueous liquid was extracted with three subsequent portions of 20 ml. of ether; the ethereal solutions, filtered and evaporated to dryness, were dried at 60° and the residue titrated with N/20 sulphuric acid, using cochineal as indicator. Tuber Aconiti, *P. Helv. V*, consists of the roots of *Aconitum Napellus* dried rapidly at about 40° and then for one hour at 50° and containing not less than 0.8% of alkaloid. The powder for administration is adjusted with lactose to contain 0.5% of alkaloid.

Farr and Wright found in aconite extract an average of 0.43% total alkaloid. The amount in the root is about twice that in the leaf. They found in dry root extract from 1.2% to 6%, English root being the best. A method of making the extract is outlined. The average yield of the dry extract was 25.9%, the ether-soluble alkaloid in this averaging 1.95%. Foreign root yielded 30% with an average of only 0.68% ether-soluble alkaloid. A standard of 1% proposed. The dose of this extract would be $\frac{1}{8}$ to $\frac{1}{4}$ grain. Foreign root is very mixed owing to mode of collection.—*Pharm. J.*, i/1913, 216.

Tinctura Aconiti (*B.P.C. '34*). An unstandardised tincture prepared by percolation of 150 g. of powdered root with 70% alcohol to 1 litre. Alcohol content, 67% to 69% *v/v* of ethyl alcohol. The tincture of the *B.P. '14* was standardised to contain 0.04% of ether-soluble alkaloids. Tinctura Aconiti I.A., prepared with 70% alcohol, contains 0.05% of total alkaloids.

Assay of Aconite Tincture and Liniment. Loss of time caused by filtering the acid liquid can be minimised thus:—Evaporate 15 ml. of liniment or 100 ml.

of tincture at low temperature to remove bulk of the alcohol. Add 5 ml. of 10% sulphuric acid. Shake with 20 ml. of petroleum ether, rinse same with water and extract with ether after making alkaline. Evaporate the ether extracts and titrate.—E. J. Chappel and N. L. Allport, *Yearb. Pharm.*, 1920, 444.

Biological Methods of Assay.

(a) **The U.S.P. X** requires a toxicity test for tincture of aconite in which a dose of not less than 0·00035 ml. and not more than 0·00045 ml. per gramme body weight must kill within 6 hours at least two of every three guinea pigs injected. The tincture is diluted with water and injected under the skin.

A toxicity test of this kind is unsatisfactory, since a repetition of the test on different groups of three animals must often give a different result. Thus if there were one hundred animals of which sixty-six would die when all were injected with the same dose of the tincture, then if these were injected three at a time some groups would include three animals which would all survive and some three which would all die.

(b) **Toxicity test on mice.** Dyer (*Quart. J. Pharm.*, 1930, 626) has suggested the determination of the toxicity by injection of a tincture into mice to find the dose which kills fifteen out of thirty mice. The toxicity, however, cannot be expressed in terms of this dose since when one sample is tested in different laboratories the dose differs (see Broom, Burn, Gaddum, Trevan and Underhill *Quart. J. Pharm.*, 1932, 33). Each sample must, therefore, be compared for toxicity with a standard, which can be prepared by mixing a series of ten samples of the dried and powdered root of *Aconitum Napellus*. This standard would have to be distributed from some central institution. By comparing a tincture prepared from the sample with that prepared from the standard and finding the dose of each which kills fifteen out of thirty mice, then if the unknown sample is more toxic than the standard, it can be adjusted by dilution so as to be equal to the standard.

ACRIFLAVINA

Acriflavina (*B.P.* '32). $C_{14}H_{14}N_3Cl, HCl = 296\cdot1$. A 2% solution in warm water, and also a 0·2% solution in warm normal saline, should remain clear and free from sediment on standing in the dark for 24 hours. Proflavine (*vide infra*) is tested for by addition of solution of formaldehyde to a 0·01% aqueous solution, when no precipitate should be formed.

The *B.P.* test for proflavine is of no value as a test for diaminoacridine hydrochloride. No result is obtained except in the presence of sulphuric acid, and if this be added a precipitate is obtained even with highly purified acriflavine. The following identity test for acriflavine is suggested:—To 5 ml. of 0·4% solution add a few drops of solution of formaldehyde and 5 ml. of 10% sodium nitrite solution; after 5 minutes, filter. The filtrate is red (distinction from euflavine and from diaminoacridine compounds).—G. F. Hall and A. D. Powell *Quart. J. Pharm.*, 1934, 522.

Commercial acriflavine consists of a mixture of approximately equal parts of the hydrochloride of 2 : 8-diaminomethylacridinium chloride and diaminoacridine dihydrochloride. The solubility of acriflavine depends on the proportions in which the two compounds are present. The methylacridinium compound has a solubility of 0·4%, and the diaminoacridine dihydrochloride of 0·3%. A synthetic mixture of equal parts has a solubility of 1%. The difference between this figure and that for acriflavine is due to the existence of diaminoacridine hydrochloride in an unstable but more soluble form. Mixtures of approximately equal parts of the two substances obtained by adding hydrochloric acid to a warm concentrated solution containing them have a solubility in agreement with the *B.P.* figure of 1 in 3.—M. Gailliot, *Quart. J. Pharm.*, 1934, 63.

From commercial samples of acriflavine containing 30% to 40% of diaminoacridine, a product containing only about 12% of this material may be obtained by treatment with caustic soda. Recrystallisation of the partly purified product from water then suffices to remove the whole of the remaining diaminoacridine.—J. Marshall, *Quart. J. Pharm.*, 1934, 514.

Results of Analysis of some Commercial Flavines

Samples of Acriflavine	"Total flavines" (ferricyanide) as acriflavine per cent.	Acriflavine from chloride (uncorr.) per cent.	Diamino- acridine dihydrochlor. (alkali pptn.) per cent.
A	97.2	96.5	35.2
B (1)	96.1	96.8	11.0
B (2)	98.6	96.7	20.0
C	93.6	94.6	42.0
Samples of Euflavine	"Total flavines" (ferricyanide) as euflavine per cent.	Euflavine from chloride corrected for NaCl per cent.	Diamino- acridine monohydro- chlor. (alkali pptn.) per cent.
A	91.4	94.2	33.5
B (1)	93.9	97.2	—
B (2)	—	—	5.5
C	87.5	95.6	25.5
Samples of proflavine	"Total flavines" (ferricyanide) as proflavine (sulphate) per cent.	Proflavine (sulphate) from sulphate per cent.	Proflavine (sulphate) (alkali pptn.) per cent.
A	92.4	89.7	92.1
B	97.7	94.4	—

—G. F. Hall and A. D. Powell, *Quart. J. Pharm.*, 1934, 522.

Euflavina (*B.P.C.* '34). $C_{14}H_{14}N_3Cl = 259.6$. Should contain not less than 93% of the pure substance, calculated with reference to the sample dried at 120° , at which temperature it should lose not more than 7% of its weight. A 0.2% solution should remain clear when kept in the dark for 24 hours. Assayed by the process of the *B.P.C.* '34: 2 g. is dissolved in and diluted with water to 750 ml. and made faintly acid to congo-red paper with N/1 hydrochloric acid, 5 g. of sodium acetate being then added; while stirring, 50 ml. of M/10 potassium ferricyanide is added and the mixture stood aside for 10 minutes, then filtered through a Buchner funnel and washed with 3 portions of 50 ml. of water; to the filtrate and washings 10 ml. of hydrochloric acid, 10 g. of sodium chloride, 1 g. of potassium iodide and a solution of 3 g. of zinc sulphate in 10 ml. of water are added and after 3 minutes the liberated iodine is titrated with standard sodium thiosulphate, standing for a further 3 minutes towards the end of the titration. A blank titration on 50 ml. of potassium ferricyanide solution is performed. 1 ml. of M/10 potassium ferricyanide is equivalent to 0.07788 g. $C_{14}H_{14}N_3Cl$.

Proflavina (*B.P.C.* '34). $C_{13}H_{11}N_3, H_2SO_4 = 307.2$. Loses not more than 10% when dried at 100° and then contains not less than 97% of $C_{13}H_{11}N_3, H_2SO_4$. 0.5 g. in 250 ml. of normal saline should remain bright when kept in the dark for 24 hours.

ADEPS

Adeps (*B.P.* '32). After the preliminary treatment described in the *B.P.*, by melting 10 to 20 g., cooling until a turbidity appears, stirring until homogeneous, and setting aside for five hours with

the container in water at 10° to 12° , or in running water for twenty-four hours, it should melt between 34° and 41° . Refractive index at 60° , 1.452 to 1.455. Acid value, not more than 1.2. Saponification value, 192 to 198. Unsaponifiable matter, not more than 0.5%. Iodine value, 52 to 66. The melting-point of the lard stearin obtained by the matter insoluble in ether at 16° to 20° should not be lower than 63° and is usually higher than 63.4° ; a low melting-point indicates the presence of beef stearin. Sesame oil is tested for by the general pharmacopœial test with hydrochloric acid containing 1% of sucrose, giving no pink colour on shaking and setting aside for 5 minutes; and cottonseed oil by the general *B.P.* test of mixing with an equal volume of a mixture of equal parts of amyl alcohol and 1% solution of precipitated sulphur in carbon disulphide and immersing the container in boiling water for 30 minutes, when no red colour develops. *Adeps, U.S.P. X*, melts at 36° to 42° , after melting just sufficiently to draw into a capillary, cooling at 10° for 24 hours or at 0° for 2 hours, and the point taken when melted just sufficiently to rise in the capillary when heated in a water-bath at about 0.5° rise per minute. It is tested for cottonseed fats by warming 5 ml. with an equal volume of alcohol containing 0.05 g. of silver nitrate and one drop of nitric acid on a water-bath for 5 minutes, when no red or brown colour nor brown line of contact develops. The microscopical appearance of the separated stearin, which should appear as flat, rhomboidal plates with one oblique end and irregularly placed, and not as cylindrical sharp-ended rods or needles in fan-shaped clusters, excludes beef fat. Saponification value, 195 to 203; iodine value, 46 to 70.

The Food and Drug Administration of the U.S. Dept. of Agriculture define lard as the rendered fresh fat from hogs, in good health at the time of slaughter, free from rancidity and containing not more than 1% of substances other than fatty acids and fats. *Leaf lard*: lard rendered at a moderately high temperature from the internal fat of the abdomen of the hog, excluding that adherent to the intestines, and with Iodine number not greater than 60. *Neutral lard*: lard rendered at low temperatures.—*S.R.A., F.D. No. 2, Rev. 4., Aug. 1933.*

Lard is very fully standardised because it is very easily adulterated and if any standards at all are given they should be as many as will give the greatest assurance that genuine lard is being used. The directions for the treatment of the sample before determining the melting-point are complicated but do not go far enough because the method adopted for the preliminary treatment may seriously affect the result. The melting-point range does not include all genuine lards.—*N. Evers, Pharm. J., i/1933, 196.*

Sevum (*B.P. '32*). M.p., 45° to 50° (by introducing into a capillary 0.75 to 1 mm. diameter, and if by melting, cooling at 0° for 2 hours or standing for 24 hours, and taking the temperature at which the substance is completely transparent). Refractive index at 60° , 1.449 to 1.451. Acid value, not more than 2.0. Saponification value, 192 to 195. Iodine value, 33 to 46. *Sevum Præparatum, U.S.P. X*, melts at 45° to 50° ; saponification value, 193 to 200; iodine value, 33 to 48.

ADRENALINA

Adrenalina (*B.P. '32*). $C_9H_{13}O_3N=183.1$. M.p., 205° to 212° with decomposition (the rate of rise of temperature being 10° per minute). The Pharmacopœia specifies the specific

otation of a 4% *w/v* solution in normal hydrochloric acid to be -50° to -53° ; this constant was not included in the 1914 Pharmacopœia.

Biological Methods of Determination.

Biological methods for the estimation of adrenaline are not required in any of the pharmacopœias since adrenaline is a chemical substance with well-defined chemical properties. Nevertheless biological tests are often applied to adrenaline to determine whether a particular sample is entirely pure or whether its activity corresponds, for example, to only 90% of that of the pure substance. The estimation of adrenaline on the blood pressure of the spinal cat is sufficiently accurate to detect differences of 5% or 6%.

(a) **Estimation of the blood pressure.** A cat is anæsthetised with chloroform and the spinal cord is exposed by removing the laminae of the second cervical vertebra. The spinal cord is divided and the brain is destroyed by passing a probe through the foramen magnum. The anæsthetic can then be discontinued, though the circulation is only maintained so long as artificial respiration is given. The blood pressure is recorded by placing a cannula in the carotid artery, and a cannula is placed in the jugular vein to give injections. In the cat so prepared the blood pressure is low and steady, and well suited for comparing the pressor (blood pressure raising) effect of different doses of adrenaline. A sample of pure adrenaline is taken as standard and a solution of strength 1 in 40,000 in saline acidified with hydrochloric acid is prepared. A similar solution of the unknown sample is prepared. Doses of 0.3 or 0.4 ml. are then injected, using the standard and the unknown alternately, in order to discover what amount of the unknown produces the same effect as a given amount of the standard.

(b) **Estimation on the isolated intestine.** A strip of the intestine of the rabbit is suspended in Ringer's solution; one end is fixed and the other is attached by a thread to a lever so that the movements of the strip are recorded by the lever on a smoked drum. In Ringer's solution supplied with oxygen and maintained at 37° , the strip alternately contracts and relaxes. If adrenaline is added to the bath the contractions are lessened or abolished according to the dose; when the adrenaline is removed the contractions begin again. An unknown solution of adrenaline can be compared with a known solution by using this property of inhibiting the movements.

Ewin's Colorimetric Test. Potassium persulphate is added to produce a concentration of 0.1% and the mixture placed in a boiling water bath. A red colour is produced. This shows adrenaline in a dilution of 1 in 5 million.—H. Dryerre, *Chem. & Drugg.*, i/1922, 418.

Colorimetric determination in extracts of suprarenal glands gives results comparable with the biological test. Gland extracts at pH 5.4 and containing 0.01 to 0.1 mg. of adrenaline are mixed with an equal volume of the reagent containing potassium persulphate, 0.2%; sodium chloride, 1%; sodium phosphate, 0.239%; and sodium acid phosphate, 0.937%. The increase in red colour, determined with a tintometer, during 30 minutes at 22° is proportional to the adrenaline content.—J. H. Barker, C. J. Eastland and N. Evers, *Biochem. J.*, 1932, 2129.

Urine, Adrenaline in. Determined colorimetrically by the red colour produced on treating it successively with sulphanilic acid, nitrous acid and ammonia. Precipitate with lead acetate and remove excess of lead by ammonium sulphate. The determination is carried out on two portions, one of which has been treated with ferric chloride at 50° to destroy adrenaline, the difference giving adrenaline content. By this method normal supplies were found to contain 0.2 to 0.4 mg. per 100 ml., larger variations occurring in pathological urines.—*J. biol. Chem.*, 1923, 57, 497, *J. chem. Soc. Abstr.*, ii/1924, 75.

SODIUM THIOSULPHATE prevents discoloration of adrenaline solutions.—*Pharm. J.*, ii/1924, 204.

Extract of Suprarenal Cortex.

Biological Method of Assay. The potency of extracts of suprarenal cortex was first demonstrated by showing that they were able to prolong the life of cats or dogs from which the suprarenal glands were removed. This method is still used, but it suffers from the drawback that several animals are needed for testing each extract, and after the animals have been kept for 3 weeks from the time of removal of the glands it is uncertain whether some small portion of gland has regenerated or not. Very commonly rats are used, since provided they are young,

they die after removal of the suprarenals. To test an extract, eighteen rats consisting of six groups of three litter mates, may be taken. The suprarenals are removed under ether anæsthesia, and from the day following the operation two of each group of three are injected, using different doses of the unknown extract. Thus, of the eighteen rats, six are kept as uninjected controls, six receive a given dose of the extract, and six receive twice that dose. The controls usually die from 4 to 12 days after the operation; the injected rats should grow, the growth rate being proportional to the dose injected. This method is, however, far from satisfactory.

Cortin. The hormone has now been isolated in a pure crystalline condition, free from traces of adrenaline. The crystals appear to have the formula $C_{20}H_{30}O_5$ and its properties point to its being an α -hydroxyaldehyde existing in two forms: a monomolecular form soluble in water and having aldehydic properties, and a polymeric form insoluble in water and not possessing aldehydic properties. Both forms appear to have the same physiological activity and will keep suprarenalectomised animals in normal condition.—E. C. Kendall and co-workers (Mayo Clinic), per *Brit. med. J.*, ii/1934, 363.

ÆTHER

Æther (*B.P.* '32). $(C_2H_5)_2O = 74.08$. The boiling-range should be 34° to 36° and the specific gravity should be from 0.720 to 0.724. It should comply with limit tests for peroxides and residue on evaporation. A test by which water heated with it should have a pH value of 4.9 to 5.1 replaces the reddening or bleaching of litmus paper test for sulphurous or other free acids in the *B.P.* '14. **Æther, U.S.P. X**, boils at about 35° and has a sp. gr. of 0.713 to 0.716 at 25° . Tests for acidity, residue, foreign odour on evaporation, aldehyde and peroxide are specified.

The acidity test is valueless since the variation tolerated (0.2 pH) is of the same order of magnitude as the experimental error.—C. Morton, *Pharm. J.*, i/1933, 3; W. H. Linnell, *ibid.*, 107.

A British Standard Specification (*B.S.S. No.* 579—1934) has been issued by the British Standards Institution for Technical Ether. The specification includes requirements regarding description, sp. gr. (not exceeding 0.725 at $15.5^\circ C$), distillation, residue on evaporation, acidity, peroxides (titanium oxide test), sulphur compounds and sampling, and the appendices describe the methods and apparatus to be used.

A sample of ordinary 0.720 ether from S.V.M. gave nearly 24 parts of acetone per 10,000. As a *qualitative* test **Rothera's Nitro-Prusside Test** may be used. 5 ml. of ether, 1 ml. of 5% sodium nitro-prusside solution and 3 ml. of strong ammonia are shaken together. Then solid ammonium chloride is added, *q.s.* to supersaturate, and the whole shaken. Samples will show a slight reaction or none at all.—A. J. Jones, *Yearb. Pharm.*, 1919, 403.

Scott Wilson's Reagent. Dissolve mercuric cyanide, 0.5 g., and sodium hydroxide, 9 g., in water, 60 ml., and add with constant stirring 20 ml. of 0.727% silver nitrate solution. No turbidity should develop on shaking the ether with excess of the reagent.

For quantitative determination employ Scott Wilson's method.—*J. Physiol.*, 1907, 444.

Æther Anæstheticus (*B.P.* '32). The boiling-range is limited to 34° to 35° . No foreign odour is perceptible on evaporation; no brown or red colour of peroxides is produced when shaken with potassium iodide and starch solution in a completely filled bottle and set aside in the dark for half an hour; presence of acetone and aldehyde is eliminated by no colour or turbidity being produced when shaken and set aside with Nessler's reagent; and no reaction for methanol is given by water shaken with it. **Æther, U.S.P. X**, is only to be used for anæsthesia when preserved in small well-closed containers and the original container must not have been opened more than 24 hours.

The difference between Æther and Æther Anæstheticus is the difference between two fractions from the same distillation. Anæsthetic ether is prepared from a fraction containing less than 0.5% of alcohol. Ether is prepared from fractions containing more than 0.5% of alcohol, a denaturant, usually 5% of wood spirit, being added. Only anæsthetic ether should be official.—W. H. Innell, *Pharm. J.*, i/1933, 106.

Peroxides in Anæsthetic Ether. The exclusion of light is the most important factor in the rate of formation of peroxide. Amber bottles are suitable. The most effective substance for retarding the formation of peroxide is pyrogallol (0.01%).—G. Middleton, *Yearb. Pharm.*, 1924, 615.

Decomposition, with formation of peroxides, prevented by addition of grain of hydroquinone to 4 oz. of ether. One part of hydroquinone to 5,000 parts of ether is sufficient.—H. O. Nolan, *Lancet*, ii/1933, 129.

Powdered iron, 1 g. per 100 ml. of freshly distilled ether, prevents formation of peroxides.—*Pharm. J.*, ii/1927, 434.

JORRISON'S REAGENT (0.4 g. of vanadic acid in 4 ml. of sulphuric acid and 6 ml. water) gives a red colour with ether if peroxides are present. Aldehydes and unsaturated alcohols give a blue colour on keeping.—*J. chem. Soc. Abstr.*, /1924, 706.

Ferrous Thiocyanate Test. To ether, 5 ml., add N/10 potassium thiocyanate solution, 1 ml., and fresh 5% ferrous ammonium sulphate solution, 1 drop. If peroxide be present a pink or red tinge develops almost immediately.—C. H. Hocking, per *Chem. & Drugg.*, i/1927, 592. See also *Yearb. Pharm.*, 1924, 615.

Determination of minute quantities of peroxides. The following method is stated to be accurate for less than one part per million of ethyl peroxide. Place 10 ml. of the sample and 20 ml. of dehydrated alcohol in a 250 ml. stoppered flask, and add a freshly prepared solution of cadmium iodide, 1 g., and potassium iodide, 1 g., in 5 ml. of acetic acid (36%). Mix thoroughly and allow to stand for one hour in the dark. Conduct a blank experiment on the reagents simultaneously. If any yellow tint is visible, titrate with N/50 sodium thiosulphate (prepared with CO₂-free distilled water). Towards the end of the titrations stopper the flasks and shake vigorously. Each ml. of N/50 sodium thiosulphate is equivalent to 9.008 parts of (C₂H₅)₂O₂ per million.—L. W. Green and R. E. Choetzwow, *J. Amer. pharm. Ass.*, 1933, 412.

Historical. Some doubt seems to exist as to who actually used ether first. Previously we stated W. T. G. Morton was the first administrator—Oct. 16th, 1846, at the Massachusetts General Hospital. Haydn's Dict. of Dates states Dr. C. J. Jackson, of Boston, first gave it to produce insensibility to pain, and directed Morton in its first use in surgery. Now it appears the credit is due to Crawford Williamson Long, who first administered ether as an anæsthetic to his patient, Mr. William Venables, on March 30th, 1842, in Jeffersonville, Georgia.

Æthylenum (B.P. '32). C₂H₄=28.03. Not more than 2% by volume of gas remains when a volume equivalent to 1000 to 1500 ml. is passed into a gas pipette containing fuming sulphuric acid or bromine solution and the residual gas treated with potassium hydroxide solution, corresponding to not less than 8% by volume of C₂H₄; absence of carbon monoxide in the gas remaining is shown by no further contraction of volume occurring, after treating first with alkaline solution of pyrogallol, when it is treated with freshly prepared acid cuprous chloride solution. Tests for limit of carbon dioxide, acid and sulphur dioxide, acetylene, phosphine, aldehydes and hydrogen sulphide and carbon monoxide are included.

Æthylis Chloridum (B.P. '32). C₂H₅Cl=64.50. Contains not less than the equivalent of 99.5% w/w of C₂H₅Cl. The assay by digestion with N/2 alcoholic potassium hydroxide in a water-bath for thirty minutes is incomplete; it is best conducted by introducing about 1.5 g. into a stoppered bottle containing 10 ml. of N/1 alcoholic potassium hydroxide, weighed accurately, and heating in a water-bath for at least 1 hour; titrate the excess of alkali with N/2 hydrochloric acid to phenolphthalein; conduct a blank experiment for an identical time using a bottle of exactly similar glass. During evaporation no foreign odour is at any time detectable and the residue is not more than 0.01%. Tests for limit of acidity, alkalinity, ionisable chlorides and ethyl alcohol are included. Æthylis Chloridum, U.S.P. X, is not assayed; tests for chloride, neutrality, alcohol, foreign volatile matter and residue on evaporation are included.

AGAR

Agar (*B.P.* '32). Yields not more than 5% of ash. It should be soluble when boiled with 100 parts of water, yielding a stiff jelly on cooling. Should yield no precipitate on addition of tannic acid to a hot 0.2% solution. 10 ml. of a rapidly cooled 0.2% aqueous solution gives a pale yellow colour with one drop of N/10 iodine and a dark purple coloration with 0.5 ml.; on setting aside for two hours, 0.5 ml. of the iodine solution gives a brownish colour. The *U.S.P. X* substance contains not more than 1% of foreign organic matter; acid insoluble ash, not more than 1%; moisture limit, 16%. A solution of 0.1 g. in 100 ml. of boiling water, on cooling, gives no precipitate with tannic acid and no blue colour with iodine.

ALCOHOL

Alcohol (*B.P.* '32). Contains from 94.7% to 95.2% *v/v* or 92.0% to 92.7% *w/w* of C_2H_5OH . Sp. gr., 0.815 to 0.817. Refractive index at 20°, 1.3637 to 1.3639. Limit tests for acidity, alkalinity, oily or resinous substances, fusel oil and allied impurities, and aldehyde are included. Absence of methyl alcohol is shown by the *B.P.* test: 5 ml. of a 10% aqueous dilution is mixed with 2 ml. of a solution of potassium permanganate in phosphoric acid and set aside for 10 minutes, after which 2 ml. of solution of oxalic and sulphuric acids is added and to the colourless solution 5 ml. of decolorised magenta solution is added; no colour is produced within 10 minutes. Industrial methylated spirit gives a deep violet coloration within 5 minutes by this test. Residue on evaporation and drying at 100°, not more than 0.01% *w/v*. The official alcohol of the *U.S.P. X* contains not less than 92.3% *w/w* or 94.9% *v/v* of C_2H_5OH at 15.56°. No violet tint should be produced within one minute when 5 ml. mixed with 2 ml. of sodium hydroxide solution, and 5 drops of 2% sodium nitroprusside solution, is made just acid with acetic acid, indicating the absence of acetone. Tests for alkaloids, diethyl phthalate, formaldehyde, isopropyl alcohol and phenols are also included.

A British Standard Specification (*B.S.S. No. 507—1933*) has been issued by the British Standards Institution for ethyl alcohol. The specification includes requirements regarding description, strength, miscibility with water, residue on evaporation, acidity, aldehyde content and sampling, and the appendices describe the methods and apparatus to be used. This alcohol is 66° O.P. (91.95% by weight or 94.68% by volume) or from 61° to 68° O.P. (91.83% to 95.81% by volume) if agreed between purchaser and vendor.

The strength of alcohol is usually expressed in terms of vol. %, though the Board of Customs and Excise favour "proof" terms. Rebate claims on Immature Spirit must be made in terms of proof gallons and hundredths of a proof gallon.

ALCOHOL DILUTION RULES

If *V* be the volume percentage of the stronger alcohol and *v* that of the weaker alcohol required—

I. *By volume.* Mix v volumes of the stronger alcohol with distilled water, s ., after cooling to make V volumes, e.g. to make an alcohol 43% from alcohol 95% take 43 volumes of the 95% and make up to 95 volumes. (See also appendix III, *B.P.C.* '34, for temperature correction tables.)

II. *By weight.* Proceed on the same lines by weight throughout.

To Transpose Volume per cent. of Alcohol into Weight per cent.

The volume per cent. is multiplied by 0.7938, and the product divided by the sp. gr. of the liquid, e.g., $80.22\% \text{ v/v} = \frac{80.22 \times 0.7938}{0.863} = 73.7875\% \text{ w/w}$

To express the weight per cent. as volume per cent. divide the weight per cent. by 0.7938 and multiply by the sp. gr. of the liquid, e.g., $90.29\% \text{ w/w}$
 $\text{by weight} = \frac{90.29 \times 0.822}{0.7938} = 93.49\% \text{ v/v}.$

To State Volume per cent. as Alcohol of Proof Strength. Multiply V per cent. by 1.753 and deduct 100 from the product. Thus $65\% \text{ v/v}$
 $= 65 \times 1.753 - 100 = +13.945^\circ$ over proof. Further, alcohol of $25\% \text{ v/v}$
 $= 25 \times 1.753 - 100 = -56.175^\circ$ proof, i.e., 56.175° under proof.

(*B.P.* 1885 stated: Proof spirit = about 57% $\text{C}_2\text{H}_5\text{OH}$ by vol., i.e., 57 parts alcohol with water produce 100 parts proof spirit.)

∴ 1 part pure alcohol $= \frac{100}{57} = 1.753$ (about) parts proof strength.

Conversely, to State Alcohol of Proof Strength as Volume per cent.:—

Add 100 to the proof strength and divide the product by 1.753; thus,

$$13.945^\circ \text{ o.p.} = \frac{113.945}{1.753} = 65\% \text{ by vol., and}$$

$$56.175^\circ \text{ u.p.} = \frac{100 - 56.175}{1.753} = 25\% \text{ by vol.}$$

To Convert Proof Gallons to Bulk Gallons multiply by:—

$$\frac{\text{Proof Strength} + 100}{100}$$

100 vols. of alcohol 90% (approx. 58° o.p.) are equivalent to 158 vols. of proof spirit.

“Proof Spirit” has sp. gr. 0.920. This, formerly, was found to be the weakest spirit that could be put to the proof of igniting a little gunpowder moistened with it. If the spirit caught fire and inflamed the gunpowder, it was designated “over proof,” and if not, “under proof.” By the Hydrometer Act, 58 Geo. III., cap. 28, Proof Spirit is defined as spirit of strength which, at a temperature of 51°F. , weighs exactly twelve-thirteenths of an equal quantity of distilled water.

Laws governing the molecular combination of alcohol with water.—*Pharm.* *U.S.*, i/1910, 754.

The following Table, founded on *B.P.* 1898 and Gilpin's Tables, shows:—

(i) The volume of distilled water necessary to be added to 100 volumes of alcohol (90%) for the production of each strength of diluted alcohol.

(ii) The volumes of alcohol (90%), and of distilled water respectively which, when mixed and reduced to 60°F. (15.5°C.), will produce, allowing for contraction in volume, 1000 ml., 1 pint, or 1 gallon of each strength of diluted alcohol.

The sp. gr. and the exact Excise (Sikes') strength at 60°F. (15.5°C.), in degrees over proof (O.P.) and under proof (U.P.), of each dilution, are given in the first column.

Table for the Dilution of Alcohol (90%) to Weaker Strengths

Volume Percentage, Specific Gravity, and Excise Strength	Alcohol (90%)	Distilled Water	Volume Produced
70 % Sp. gr. 0·8900 22·7 O.P.†	100 vols. + 31·05 vols. 777·8 ml. + 241·6 ml. *648·5 g. + 241·6 g. 15 oz. 266 m. + 4 oz. 398 m. 124 oz. 215 m. + 38 oz. 307 m. *6 lbs. 7 ⁷ / ₈ oz. + 2 lbs. 6 ⁵ / ₈ oz.		= 128·57 vols. = 1000 ml. = 1000 ml. = 1 pint = 1 gal. = 8 lbs. 14 ¹ / ₂ oz.
60 % Sp. gr. 0·9135 5·20° O.P.†	100 vols. + 53·65 vols. 666·7 ml. + 357·8 ml. *555·9 g. + 357·8 g. 13 oz. 160 m. + 7 oz. 74 m. 106 oz. 320 m. + 57 oz. 112 m. *5 lbs. 9 oz. + 3 lbs. 9 ¹ / ₄ oz.		= 150 vols. = 1000 ml. = 1000 ml. = 1 pint = 1 gal. = 9 lbs. 2 ¹ / ₄ oz.
45 % Sp. gr. 0·9436 21·2° U.P.†	100 vols. + 105·34 vols. 500 ml. + 526·6 ml. *417·2 g. + 526·6 g. 10 oz. + 10 oz. 256 m. 80 oz. + 84 oz. 130 m. *4 lbs. 2 ⁷ / ₈ oz. + 5 lbs. 4 ¹ / ₂ oz.		= 200 vols. = 1000 ml. = 1000 ml. = 1 pint = 1 gal. = 9 lbs. 7 oz.
20 % Sp. gr. 0·9760 64·9° U.P.†	100 vols. + 355·8 vols. 222·2 ml. + 790·7 ml. *185·2 g. + 791 g. 4 oz. 213 m. + 15 oz. 390 m. 35 oz. 267 m. + 126 oz. 243 m. *1 lb. 13 ³ / ₄ oz. + 7 lbs. 14 ¹ / ₂ oz.		= 450 vols. = 1000 ml. = 1000 ml. = 1 pint = 1 gal. = 9 lbs. 12 ¹ / ₄ oz.

NOTE.—*These figures are the weights necessary to produce a gallon and a litre respectively, at 15·5° C. † Stevenson.

Amount of Ethylic Alcohol by Volume in Various Liquors.

Whisky	White Wine	12% to 14%
Rum	Champagne	10% to 13%
Gin	Orange Wine	10% to 12%
Strong Liqueurs ..	Burgundy	9% to 12%
Proof Spirit .. 57%	Hock	9% to 12%
Brandy 43% to 57%	Claret	8% to 12%
Port 20% to 30%	Cider	5% to 9%
White Wine (strong) 23% to 29%	Strong Ale or Stout ..	5% to 9%
Sherry 16% to 22%	Beer and Porter ..	2% to 5%
Madeira 16% to 22%		—HALE WHITE.

The above are pre-war.

The current strengths are: Whisky, Rum, Gin and Brandy, 40% to 47%; Strong Liqueurs, 43% to 47%; Proof Spirit, 57·1%; Port, 16% to 22%; Sherry, 16% to 22%; Madeira, 16% to 22%; White Wine, 12% to 14%; Champagne, 10% to 13%; Orange Wine, 12% to 15%; Burgundy, 12% to 14%; Hock, 12% to 14%; Claret, 10% to 14%.

Mountain Dew Scotch Whisky. 40·1% Alcohol by volume, total extractive 0·15%, ash 0·01%; volatile acidity (as acetic) 19·4 per 100,000 of absolute alcohol, furfural 0·6 ditto, esters (as ethyl acetate) 44 ditto, aldehyde 22· ditto.—*Lancet*, ii/1923, 1036.

British wines and temperance drinks. A few of the ordinary non-alcoholic wines were found to contain a little more than 2%. A sample of raspberry wine contained 3·28%.—G. C. Hancock, Min. Health Report, No. 24, *Brit. med. J.*, i/1924, 1,143.

Analysis of Wines. *P. Helv. V* gives a useful summary.

ETHYL ALCOHOL TABLE.

As employed in the Government Laboratory.

Gr. °C.	Wt. per cent.	Vol. per cent.	Sp.Gr. at 15·5°C.	Wt. per cent.	Vol. per cent.	Sp.Gr. at 15·5°C.	Wt. per cent.	Vol. per cent.	Sp.Gr. at 15·5°C.	Wt. per cent.	Vol. per cent.
99	0·53	0·66	0·947	36·00	42·95	0·895	60·23	67·92	0·843	82·00	87·09
98	1·07	1·34	0·946	36·54	43·54	0·894	60·66	68·33	0·842	82·40	87·42
97	1·61	2·02	0·945	37·07	44·13	0·893	61·09	68·74	0·841	82·80	87·74
96	2·17	2·71	0·944	37·60	44·71	0·892	61·52	69·14	0·840	83·20	88·06
95	2·73	3·42	0·943	38·12	45·28	0·891	61·95	69·55	0·839	83·60	88·37
94	3·31	4·14	0·942	38·64	45·85	0·890	62·38	69·95	0·838	83·99	88·68
93	3·90	4·88	0·941	39·15	46·40	0·889	62·81	70·35	0·837	84·39	88·99
92	4·51	5·63	0·940	39·65	46·95	0·888	63·24	70·75	0·836	84·78	89·30
91	5·13	6·40	0·939	40·15	47·50	0·887	63·67	71·15	0·835	85·17	89·61
90	5·76	7·18	0·938	40·65	48·04	0·886	64·10	71·55	0·834	85·56	89·91
89	6·41	7·98	0·937	41·15	48·57	0·885	64·53	71·95	0·833	85·95	90·22
88	7·08	8·80	0·936	41·64	49·10	0·884	64·96	72·34	0·832	86·34	90·52
87	7·76	9·65	0·935	42·13	49·63	0·883	65·39	72·74	0·831	86·73	90·82
86	8·46	10·51	0·934	42·62	50·15	0·882	65·81	73·13	0·830	87·11	91·11
85	9·18	11·40	0·933	43·11	50·67	0·881	66·24	73·52	0·829	87·50	91·40
84	9·91	12·29	0·932	43·59	51·18	0·880	66·66	73·91	0·828	87·88	91·69
83	10·65	13·20	0·931	44·06	51·68	0·879	67·09	74·30	0·827	88·27	91·98
82	11·42	14·13	0·930	44·53	52·18	0·878	67·51	74·68	0·826	88·65	92·26
81	12·20	15·08	0·929	45·00	52·67	0·877	67·93	75·06	0·825	89·03	92·55
80	12·99	16·04	0·928	45·47	53·16	0·876	68·35	75·44	0·824	89·41	92·83
79	13·80	17·02	0·927	45·94	53·65	0·875	68·77	75·82	0·823	89·79	93·11
78	14·61	18·00	0·926	46·40	54·14	0·874	69·19	76·19	0·822	90·16	93·38
77	15·43	18·99	0·925	46·87	54·62	0·873	69·62	76·57	0·821	90·53	93·65
76	16·25	19·98	0·924	47·33	55·10	0·872	70·04	76·94	0·820	90·90	93·92
75	17·08	20·97	0·923	47·79	55·58	0·871	70·46	77·32	0·819	91·27	94·19
74	17·90	21·96	0·922	48·25	56·05	0·870	70·88	77·69	0·818	91·63	94·45
73	18·72	22·94	0·921	48·71	56·52	0·869	71·30	78·06	0·817	92·00	94·71
72	19·53	23·91	0·920	49·17	56·99	0·868	71·72	78·43	0·816	92·36	94·97
71	20·34	24·85	0·919	49·63	57·46	0·867	72·14	78·80	0·815	92·72	95·22
70	21·14	25·83	0·918	50·08	57·92	0·866	72·55	79·17	0·814	93·08	95·47
69	21·93	26·77	0·917	50·53	58·38	0·865	72·97	79·53	0·813	93·44	95·72
68	22·71	27·69	0·916	50·98	58·83	0·864	73·39	79·89	0·812	93·80	95·97
67	23·48	28·69	0·915	51·43	59·29	0·863	73·81	80·25	0·811	94·15	96·21
66	24·23	29·48	0·914	51·88	59·74	0·862	74·22	80·61	0·810	94·50	96·45
65	24·97	30·34	0·913	52·33	60·19	0·861	74·64	80·97	0·809	94·85	96·69
64	25·68	31·18	0·912	52·77	60·63	0·860	75·05	81·32	0·808	95·20	96·93
63	26·37	31·99	0·911	53·21	61·07	0·859	75·47	81·68	0·807	95·55	97·16
62	27·06	32·79	0·910	53·65	61·51	0·858	75·88	82·03	0·806	95·89	97·39
61	27·73	33·56	0·909	54·10	61·95	0·857	76·30	82·38	0·805	96·23	97·62
60	28·39	34·33	0·908	54·54	62·39	0·856	76·71	82·73	0·804	96·57	97·84
59	29·03	35·06	0·907	54·98	62·83	0·855	77·12	83·08	0·803	96·91	98·06
58	29·66	35·79	0·906	55·42	63·26	0·854	77·53	83·42	0·802	97·25	98·28
57	30·28	36·50	0·905	55·87	63·70	0·853	77·94	83·77	0·801	97·59	98·49
56	30·90	37·20	0·904	56·31	64·13	0·852	78·35	84·11	0·800	97·91	98·70
55	31·50	37·89	0·903	56·75	64·56	0·851	78·76	84·44	0·799	98·24	98·91
54	32·09	38·57	0·902	57·18	64·98	0·850	79·17	84·78	0·798	98·57	99·12
53	32·67	39·22	0·901	57·62	65·41	0·849	79·58	85·12	0·797	98·90	99·32
52	33·25	39·87	0·900	58·06	65·83	0·848	79·98	85·46	0·796	99·22	99·52
51	33·81	40·50	0·899	58·50	66·25	0·847	80·39	85·80	0·795	99·55	99·72
50	34·37	41·13	0·898	58·93	66·67	0·846	80·79	86·12	0·794	99·87	99·92
49	34·92	41·74	0·897	59·37	67·08	0·845	81·20	86·44	0·79359	100·00	100·00
48	35·46	42·35	0·896	59·80	67·50	0·844	81·60	86·77			

Spirit tables for use with Sikes' A and B Hydrometers, issued by the Commissioners of H.M. Customs and Excise for use in connection with "The Strength and Weight of Spirits Ascertainment Regulations, 1930," are available (H.M. Stationery Office).

Alcohol Limits of B.P. Galenicals. Insufficient allowance has been made for moisture in the air-dry drug and for the volume occupied by the solid ex-

tractive. Revised limits are suggested for the majority of preparations.—T. Cocking, *Quart. J. Pharm.*, 1934, 76.

Alcohol in the body. The human body normally contains about 0·003% alcohol. Excess of 0·01% indicates that alcohol has been taken recently. If analysis is made from 2 to 6 hours after taking alcohol and the result multiplied by the bodyweight it will give approximately the total of alcohol taken. The presence of 0·4 to 0·5% represents a condition of drunkenness and means that about 300 g. of alcohol has been taken—this would be present in about a pint of whisky; twice this amount will cause death.—*J. Amer. med. Ass.*, ii/1928, 1928.

Tables giving the caloric values of a glass of the various wines, spirits and liquors. Those who give up sugar in their tea for the sake of their figure should logically abstain from alcohol: it is not uncommon, however, to see them consume at dinner one glass of sherry=3 lumps of sugar, 2 glasses of champagne=6 lumps of sugar, one glass of Benedictine=6 lumps of sugar, making a total of 19 lumps of sugar=380 calories.—W. F. Christie, *Practitioner*, ii/1932, 723.

Determination of Alcohol in Blood. Widmark's method is the most satisfactory. This employs a small stoppered conical flask with a small glass tube attached to a glass rod projecting from the stopper. 1 ml. of a solution of 0·25 g. of potassium dichromate in 1 ml. of water and 99 ml. of sulphuric acid is placed in the flask, and 0·2 ml. of blood in the cup. The stoppered flask is heated to 50° to 60° for 2 hours. The alcohol evaporates from the blood and is absorbed by the acid, reducing the dichromate. At the end of the heating, 25 ml. of water is added and 0·5 ml. of 5% potassium iodide solution. After exactly 1½ minutes the iodine is titrated with N/100 sodium thiosulphate. Two blanks are carried out simultaneously. 1 ml. N/100 thiosulphate=0·000113 g. alcohol. Normal alcohol content of blood is 0·003%; a content of 0·16% indicates a distinct influence of alcohol on the subject and values of over 0·2% show definite alcoholism. Except in cases of acetonæmia the amount of alcohol consumed may be calculated fairly accurately from the formula: amount of alcohol in grammes=body weight in kilogrammes \times 6·8 (blood alcohol per cent. + number of hours after the last dose of alcohol \times 0·015). The results are more accurate than those calculated from the percentage of alcohol in the urine.—A. Heiduschka and E. Floto, *Pharm. Zentralh.*, 1933, 329.

Diethyl Phthalate. A British Standard Specification (B.S.S. No. 574—1933) has been issued by the British Standards Institution for diethyl phthalate. The specification includes requirements regarding description, specific gravity (1·114 to 1·129 at 15·5°), refractive index (1·4805 to 1·506 at 20°), water, ash, acidity, ester content (not less than 98% w/w) and sampling, and the appendices describe the methods and apparatus to be used.

DETECTION OF DIETHYL PHTHALATE IN ALCOHOLIC LIQUIDS. The following test of the Bureau of Internal Revenue of the U.S. Treasury Department was found satisfactory:—(a) In presence of considerable amount. To 10 ml. of sample add 2 ml. of 10% NaOH and evaporate to dryness on the steam-bath. Add 5 ml. of conc. sulphuric acid and 0·025 g. of resorcinol and heat for 5 minutes on the steam-bath. Transfer to a test-tube, heat in oil bath at 160° for 5 minutes, cool, pour into excess of alkaline water. A greenish yellow fluorescence (due to fluorescein) is produced.

(b) In presence of traces. To not less than 50 ml. add 0·2 ml. of 10% NaOH and proceed as above. Allow the dilute fluorescein solution to stand 24 hours and view through the long axis of a Nessler glass. A blank test on pure alcohol should be made for comparison since a fluorescence is produced in the absence of diethyl phthalate which fades in 24 hours.—J. A. Hardy & L. F. Hoyt, *J. Amer. pharm. Ass.*, 1925, 219.

Alcohol Amylicum (B.P.C. '34). $C_5H_{12}O$ = 88·09. Boiling-range 128° to 132°. Sp. gr., 0·815 to 0·817. Acidity as $CH_3 \cdot COOH$, not more than 0·01%.

The amyl alcohol now used in the Gerber process is commercial amyl alcohol obtained from fusel oil, b.p., 128° to 132°. The following requirements are suggested:—Commercial amyl alcohol, colourless to light yellow, sp. gr. at 15·5° 0·813 to 0·816; b.p., 124° to 132°; 10 ml. of the reagent should mix with 10 ml. of hydrochloric acid (sp. gr., 1·16) and the further addition of 1·0 ml. of water should cause permanent turbidity.—A. More, *Analyst*, 1933, 277.

Iso-Amyl Butyrate. $CH_3 \cdot CH_2 \cdot CH_2 \cdot COO \cdot CH_2 \cdot CH_2 \cdot CH < \begin{matrix} CH_3 \\ CH_3 \end{matrix}$ = 158·14

Colourless liquid with sp. gr. 0·882 at 0°. Used as a flavouring agent. Con

cially the article contains 78% to 93%; sp. gr. ranges from 0.853 to 0.860. Refractive index, 1.4073 to 1.4110 at 20°. B.p. about 135°.

Amylis Nitris (*B.P.* '32). $C_5H_{11}O_2N = 117.1$. Contains not less than 90% of nitrites, calculated as $C_5H_{11}O_2N$. At least 85% distils between 90° and 100°. Sp. gr., 0.874 to 0.884. Assayed by the interaction of an alcoholic dilution of potassium iodide solution and dilute sulphuric acid in a brine-charged nitrometer, and measurement of the nitric oxide produced; at 15.5° and normal pressure each millilitre of moist nitric oxide is equivalent to 0.0049 g. of $C_5H_{11}O_2N$. **Amylis Nitris**, *U.S.P. X*, contains not less than 80% by weight of $C_5H_{11}O_2N$; assayed by measurement of the nitric oxide produced after being shaken with potassium bicarbonate and diluted with alcohol. **Amylium nitrosum**, *Helv. V*, is assayed by decomposing the amyl nitrite by shaking for 5 minutes with 10 g. in 10 ml. of alcohol with 20 ml. of N/10 silver nitrate, 15 ml. of saturated solution of potassium chlorate and 5 ml. of dilute nitric acid. The mixture is filtered and 50 ml. of the filtrate is titrated with N/10 ammonium thiocyanate using iron alum as indicator. Each millilitre of N/10 silver nitrate is equivalent to 0.0351 g. of $C_5H_{11}O_2N$.

Amyleni Hydras (*B.P.C.* '34). $C_5H_{12}O = 88.09$. Boils between 97° and 103°. Sp. gr., 0.812 to 0.815. Amyl alcohol present is limited by mixing 1 part in 20 parts of water with 2 drops potassium permanganate solution, which should not be completely decolorised in 10 minutes; it should have no reducing action on ammoniacal silver nitrate and produce no blue colour with anhydrous copper sulphate, indicating absence of aldehyde and water respectively.

Alcohol Dehydratum (*B.P.* '32). $C_2H_5OH = 46.05$. Has a sp. gr. of 0.7936 to 0.7967, a refractive index at 20° of 1.3614 to 1.3618 and contains not less than 99.4% by volume or 99% by weight of C_2H_5O . **Alcohol Dehydratum**, *U.S.P. X*, containing 99% by weight of C_2H_5OH , has sp. gr. not higher than 0.798 at 15.56°.

Alcohol Isopropylicum (*B.P.C.* '34). $(CH_3)_2CHOH = 60.06$. Boils between 80.5° and 81.5° and contains about 96% *v/v* (equivalent to about 94% *w/w*) of C_3H_8O ; sp. gr., 0.810 to 0.812. It may be detected in methyl or ethyl alcohols by the production of a white or yellow precipitate on heating the liquid to be tested just to boiling with mercuric sulphate solution. It may be separated in solutions of ethyl and methyl alcohols by saturating with salt, when an upper layer of isopropyl alcohol separates.

Detection of isopropyl alcohol.--*Amer. J. Pharm.*, 1931, 341; *Analyst*, 1931, 115. Isopropyl alcohol made in Great Britain is obtained by catalytic reduction of acetone. In perfumery, it is a good plan to blend with ethyl alcohol, the odour of isopropyl alcohol being too heavy and persistent when used alone. A table of solubilities of oils and synthetic perfumes in various spirits is given.—*Chem. Drugg.*, i/1927, 11.

Normal Butyl Alcohol. A British Standard Specification (*B.S.S. No. 573—1933*) has been issued by the British Standards Institution for Normal Butyl Alcohol (Butanol). The specification includes requirements regarding description, specific gravity, distillation-range, flash-point, residue on evaporation, acidity, aldehyde content and sampling, and the appendices describe the methods and apparatus to be used.

Dibutyl Phthalate. A British Standard Specification (*B.S.S. No. 573—1934*) has been issued by the British Standards Institution for Dibutyl Phthalate (normal-butyl ester of ortho-phthalic acid). The specification includes requirements regarding description, specific gravity, refractive index, water, ash, acidity, ester content and sampling, and the appendices describe the methods and apparatus to be used.

Alcohol Methylicum (*B.P.C.* '34). $CH_3OH = 32.03$. Sp. gr. not higher than 0.799. Limit of ethyl alcohol is included by shaking with 10 volumes of 2% sodium hydroxide solution and 5 volumes of N/10 iodine solution when no turbidity or precipitate appears and no odour of iodoform develops when heated from 60° to 70° for half an hour. On acidifying with acetic acid a mixture of 5 ml. of the alcohol, 2 ml. of normal sodium hydroxide and 0.2 ml. of 2% sodium ferric prusside solution, no violet colour is produced within one minute, limiting the acetone present. It may be estimated in alcoholic mixtures by matching with a series of control concentrations when oxidised with potassium permanganate and phosphoric acid, decolorising after 10 minutes with oxalic and sulphuric acids and treating with decolorised magenta solution as described under **Alcohol**, previously making sure that the solution contains no formaldehyde.

A British Standard Specification (B.S.S. No. 506—1933) has been issued by the British Standards Institution for Methyl Alcohol (Methanol). This specification includes requirements regarding description, specific gravity, distillation range, residue on evaporation, miscibility with water, acids, aldehydes and ketones, sulphur and sulphur compounds, and sampling, and the appendices describe the methods and apparatus to be used.

Methyl and wood alcohols and acetone are markedly more toxic than ethyl alcohol. Deleterious effects of chronic alcoholism on growth.—T. Sollman, O. H. Schettler and N. C. Wetzel.—*J. Pharmacol.*, Nov., 1920. *Furze's details*, Vol. I., p. 115.

Spiritus Methylatus Industrialis (B.P. '32). Sp. gr. not greater than 0·817. Residue at 100° not more than 0·01%.

Spiritus Methylatus Industrialis sine Acetone (B.P.C. '34). Sp. gr. not greater than 0·817. An acetone limit is specified: when 5 volumes diluted with water to 10 volumes, 1 volume of 1% *o*-nitrobenzaldehyde in 5% alcohol and 1 volume of 15% sodium hydroxide solution are added the color developed in 15 minutes should not be deeper than that produced by similarly treating 10 volumes of 0·025% *v/v* solution of acetone in 50% alcohol.

Acetone. Colorimetric method for determining and detecting in spirit, based on formation of indigo when sodium hydroxide is added to a mixture of *o*-nitrobenzaldehyde and acetone; can also be used for isopropyl alcohol and its oxidation to acetone.—C. A. Adams, *Pharm. J.*, ii/1928, 604.

Mineralised Methylated Spirit. (Pyridinised). (See also Vol. I, p. 11).

The B.M.A. in July, 1924, protested against the use of pyridine as denaturant as rendering the spirit unfit for surgical use with result that the Board of Customs and Excise permitted use of Industrial Methylated Spirit (i.e. pyridinised) for medical and surgical purposes, other than internal use—under specific conditions as described in Vol. I. Older refs. on this matter in Vol. I, 18th Edn., pp. 25, 26.

METHYLATED SPIRIT AND ETHER REGULATIONS (NORTHERN IRELAND), 1928. In force from March 1, 1928.

METHYLATED SPIRIT. Retailers to keep records (in accordance with Schedules set out) of all purchases and sales. In the case of sales signature of purchaser and of introducer (if any) to be affixed, unless a signed order has been received, when the words "Signed Order" must be entered with date of sale. The order endorsed with name of seller and date of sale and kept for 2 years. When selling to another retailer enter words "Re-Sale."

METHYLATED ETHER. Wholesalers to keep records (in accordance with Schedule) of all sales of Ether and preparations, except proprietary medicines containing not more than 5%, and retailers authorised to sell such proprietary medicines; and preparations containing Ether, of formulæ sanctioned by the Ministry of Home Affairs, or on prescriptions from medical men, dentists (marked "For local dental treatment only"), or veterinary surgeons (marked "For animal treatment only"), but may not supply more than once on same prescription. Prescriptions marked with date of dispensing and kept for 2 years. Permit may be granted to sell Ether for manufacturing or scientific use. Retailers to keep Register of all purchases and sales.—*Chem. & Drug J.* i/1928, 589.

METHYLATED SPIRIT DRINKING. The popular tippie is "Biddie," a deadly mixture of wine and methylated spirit. The red wine is bought at the less reputable bars at ninepence a quart bottle; and the methylated spirit or "feek," as it is known, is brought in and mixed with the so-called wine. The result is precisely the same as that seen in the New York drunkard.

"Red Biddie" is a devil's brew from a witch's cauldron. It makes the topsoy not so much drunk as doped. Glasgow police officers state that a man or woman taken under the influence of "Red Biddie" might lie unconscious for 24 hours, and at the end of that period if they take a drink of water or any other liquid they immediately become drunk again. They are like subjects under hypnotic trance. In whatever position their limbs are placed so they remain in it. R. E. Corder, *Daily Mail*.

Vinum Xericum (B.P.C. '34). Contains not less than 16% *v/v* of ethyl alcohol. Sp. gr., 0·990 to 1·000. Total acids as tartaric acid ($C_4H_6O_6$) not less than 0·4%. It contains not more than 450 parts per million of sulphur dioxide to comply with the Public Health (Preservatives in Food) Regulations. The alcohol content is determined by method I of the British Pharmacopoeia. Dilute 25 ml. with 100 to 150 ml. of water in a 500 to 800 millilitre flask and

le pumice powder; connect by a still-head to a condenser and distil at least ml.; dilute with water to 100 ml. at the same temperature as that at which original volume was measured, determine the sp. gr. and refractive index by reference to tables calculate the percentage of ethyl alcohol in the final wine; if the refractive index differs by more than 0.0002 from that responding with the specific gravity found, saturate 75 ml. with sodium chloride and shake for several minutes with 100 ml. of light petroleum (b.p. to 60°); after standing for half an hour run off the lower layer and wash the petroleum layer with 25 ml. of brine; distil the mixed brine liquids after making just alkaline with normal sodium hydroxide to solid phenolphthalein determine specific gravity and refractive index as before. Total acids are titrated with fifth normal sodium hydroxide to phenolphthalein. Sulphur dioxide may be determined by boiling for 10 minutes 500 ml. of water and 20 ml. of hydrochloric acid in a round-bottomed litre flask, which is connected with a water-cooled reflux condenser of which the upper end connects with two absorption flasks in series each containing 10 ml. of hydrogen peroxide solution, and maintaining a current of carbon dioxide (passed through sodium carbonate solution) through the apparatus during the whole process; contents of the flask are cooled and 50 to 100 grammes of the wine introduced as quickly as possible and boiled for 45 minutes; the absorption flasks are disconnected and the contents titrated with N/10 sodium hydroxide using mophenol blue as indicator, and subtracting the amount of standard sodium hydroxide required to neutralise 20 ml. of the hydrogen peroxide solution to mophenol blue.

ALOE

Aloe (*B.P.* '32). Loss at 100° not more than 10%. Ash not more than 5%. Aloes, in powder, complies with the standard for unground drug. On boiling with 100 parts of water until nearly dissolved, cooling, adding 1 part of diatomite and filtering, 10 ml. of the filtrate with 2 ml. of nitric acid gives a yellow-brown colour changing quickly to vivid green in the case of Cape aloes, Curaçao aloes gives a deep brownish red, in the case of the Socotrine variety a pale brownish yellow and with Zanzibar aloes a yellowish-brown colour is produced. In the *U.S.P. X* the Socotrine, Curaçao and Cape varieties are official. Aloe, *U.S.P. X*, should contain not more than 4% of ash, not more than 10% of moisture, and not less than 50% of water-soluble extractive determined by macerating 2 g. with 70 ml. of water, shaking half-hourly for 8 hours and standing for 16 hours; filtering and washing to 100 ml.; evaporating 50 ml. and drying at 110°. A nearly clear solution should be obtained by heating 1 g. with 50 ml. of alcohol and then cooling. Aloe, *P. Helv. V*, contains less than 12% of moisture and 1.5% of ash. Curaçao and Natal aloes are excluded and the product contains not less than 80% of non-resinous substances soluble in a mixture of 5 parts of methyl alcohol and 30 parts of chloroform.

Extract Content in Aloes. Average content water-soluble in Barbados aloes was 60%, and in Socotrine aloes 45% approx.

The proportion of aloes or other emodin-containing drug in a preparation may be determined by extraction with ether in the presence of acid and measuring the red colour that is produced when the ether extract is made strongly alkaline with ammonia. Results are given for Socotrine, Cape and Curaçao aloes.—P. Auer and G. E. Mallory, *Amer. J. Pharm.*, 1934, 81.

Differentiation of Aloes by Quinoline Hydrogen Peroxide Reagent. 10% hydrogen peroxide is shaken with an equal volume of quinoline (synthetic). Heat is evolved. At first the quinoline forms the top layer, but, after shaking, the lower. The quinoline is separated, dried with anhydrous

sodium sulphate and filtered. Or in preference proceed more dilute. Finally dilute to 1% with more quinoline. A few mg. of finely powdered aloes moistened with the reagent and warmed to 60° for 3 to 5 minutes. *A. chinensis* and *A. vulgaris* give purple, turning rose pink on acidifying with 1% sulphuric acid; *A. Perryi* brown with hydrogen peroxide, remaining so on acidifying; *A. ferox* and *A. spicata*, and others, green with hydrogen peroxide, changing greenish yellow on adding acid.—E. J. Schorn, *Pharm. J.*, i/1930, 212: see also A. H. Ware, *ibid.*, 596.

Aloinum (B.P. '32). Ash not more than 0.5%. Water-insoluble matter more than 1.5%, by shaking frequently for 2 hours with 130 parts of water, filtering, washing with 25 parts of water, and drying at 100°. The proportion of water-insoluble matter varies greatly with the temperature of the water, samples giving less than 1.5% at 25° may yield as much as from 7% to 10% at 15°. Aloinum, U.S.P. X, leaves not more than 0.5% of ash; water-insoluble matter, not more than 1.5%. A benzene extract should not impart a pink colour to an equal volume of 5% ammonia water.

ALUMEN

Alumen (B.P. '32). $\text{KAl}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O} = 474.4$ or $\text{NH}_4\text{Al}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O} = 453.3$. Contains not less than 99.5% of the appropriate pure substance. Potash alum should not evolve ammonia when warmed with 20 ml. of water and 5 ml. of sodium hydroxide solution; and ammonia alum leaves not more than 0.5% of residue when the filtrate from 1 g. in 100 ml. of boiling water and excess of dilute ammonia solution, is evaporated and ignited. Both alums are assayed gravimetrically by precipitation as aluminium hydroxide and ignition to Al_2O_3 . Alumen, U.S.P. X, is either ammonia alum or potash alum containing 99.5% of the pure alum.

Determination of Aluminium. Aluminium may be separated quantitatively from iron by precipitating the iron as sulphide in ammoniacal tartrate solution and after removing the sulphides from the filtrate the aluminium is precipitated as aluminium hydroxyquinolate by adding a 5% solution of 8-hydroxyquinoline sulphate to the ammoniacal solution. The mixture is heated to 90°, allowed to stand and the precipitate dried and weighed.—J. Haslam, *Analyst*, 1933, 2.

Small amounts of aluminium such as in plant ashes and fruit juices may be determined by precipitating the iron and aluminium as phosphates; the precipitate is dissolved in acid, the iron removed with cupferron and the aluminium precipitated with 8-hydroxyquinoline. Full practical details of the process are included.—L. Hart, *J. Ass. off. agric. Chem.*, 1932, 285.

Alumen Exsiccatum (B.P.C. '34). $\text{KAl}(\text{SO}_4)_2 = 258.2$. Potash Alum deprived of its water of crystallisation. Determined gravimetrically it contains not less than 99.5% of $\text{KAl}(\text{SO}_4)_2$, calculated on the dried substance. Loss at 200° not more than 10% of its weight. Alumen Exsiccatum of the U.S.P. X may be either potash alum or ammonia alum heated at a temperature not exceeding 200° until aqueous vapours cease to be evolved. After drying at 200°, it contains not less than 96.5% of $\text{AlNH}_4(\text{SO}_4)_2$ or $\text{AlK}(\text{SO}_4)_2$. Assayed, after filtering out any matter insoluble in water, by precipitation as aluminium hydroxide and ignition to oxide.

Aluminii Sulphas (B.P.C. '34). $\text{Al}_2(\text{SO}_4)_3 \cdot 16\text{H}_2\text{O} = 630.4$. Assayed for Alumen, it yields Al_2O_3 equivalent to not less than 99% of $\text{Al}_2(\text{SO}_4)_3 \cdot 16\text{H}_2\text{O}$. The substance of the N.F.V. is $\text{Al}_2(\text{SO}_4)_3 \cdot 18\text{H}_2\text{O}$, of which it should contain not less than 99.5%, corresponding to a yield of 15.23% of aluminium oxide in the assay.

AMMONII CARBONAS

Ammonii Carbonas (B.P. '32). A variable mixture of bicarbonate ($\text{NH}_4\text{HCO}_3 = 79.05$) and carbamate ($\text{NH}_4\text{NH}_2\text{CO}_2 = 78.06$).

etermined by dissolving in excess standard acid, boiling, cooling and back titrating with standard alkali using methyl red as indicator, it contains the equivalent of from 30% to 32.5% of NH_3 . Residue on volatilisation, not more than 0.025%. **Ammonii Carbonas, U.S.P. X**, yields from 30% to 32% of NH_3 ; the titration is conducted without boiling and methyl orange is used as indicator. **Ammonium carbonicum, P.G. VI**, consists of ammonium carbonate or a mixture of ammonium carbonate and ammonium bicarbonate containing from about 21% to 33% of NH_3 .

Stability of Aqueous Solution. On page 140 of Vol. I data are provided by Self and Corfield's work conveying that a 1 in 8 solution was found to be stable. A 1 in 6 solution, which is commonly employed for dispensing, has been found to retain its ammonia content for 3 months.

Ammonii Bicarbonas (B.P. '32). $\text{NH}_4\text{HCO}_3 = 79.05$. Contains from 29% to the equivalent of 102% of NH_4HCO_3 , by adding excess of acid, boiling, cooling and back titrating to methyl red. Residue on volatilisation, not more than 0.01%.

Liquor Ammoniae Fortis (B.P. '32). Has a specific gravity of 0.885 to 0.891 and contains not less than 31.5% and not more than 33.5% by weight of NH_3 . Methyl red is used as indicator for titration in excess normal sulphuric acid with normal sodium hydroxide. Residue on evaporation on a water-bath, not more than 0.01% w/v. **Aqua Ammoniae Fortior, U.S.P. X**, contains from 25% to 29% of NH_3 by weight. Assayed by direct titration of the diluted water with normal sulphuric acid to methyl orange. It is directed to be assayed frequently owing to rapid deterioration. Sp. gr., about 0.897 at 25°. Residue on evaporation and drying at 120°, not more than 0.06%.

Liquor Ammoniae Dilutus (B.P. '32). An aqueous solution containing not less than 9.5% and not more than 10.5% w/w of NH_3 . Residue on evaporation on a water-bath, not more than 0.005% w/v. Sp. gr. 0.958 to 0.9615. **Ammonia Water of the U.S.P. X**, contains from 9.5% to 10.5% w/w of NH_3 , with sp. gr. about 0.958 at 25°. Residue on evaporation and drying at 120° not more than 0.02%.

Ammonii Sulphocyanidum. *Syn.* AMMONII RHODANIDUM (Thiocyanas)— $\text{H}_4\text{SCN} = 76.1$. White crystals soluble in water and alcohol. Reagent in toxicology to separate arsenic, antimony, mercury, etc., and in silver titrations.

Hydrazine. *Syn.* DIAMIDE $(\text{NH}_2)_2 = 32.05$. In the basic condition this body is not stable, but the sulphate $(\text{NH}_2)_2\text{H}_2\text{SO}_4$ is a well defined stable salt—white crystals soluble in hot water. It is a useful reducing agent, e.g., in making colloidal metal hydrosols. It has antiseptic properties, e.g., it will destroy bacteria, etc.

PHOTOGRAPHIC USE.—Caldwell discovered that the inclusion of the salts of hydrazine, or hydroxylamine, in the emulsion renders a plate practically proof against over exposure or reversal. Plates or papers treated with the hydrazine salts may also be printed right out and toned like ordinary P.O.P., or partly printed and the operation completed by development.

AMYLUM

Amylum (B.P. '32). Starch obtained from the grains of maize, *Zea Mays* Linn., only is official, in place of that from wheat, *Triticum sativum* Lam., maize, *Zea Maize* Linn., and rice, *Oryza sativa* Linn., of the 1914 Pharmacopœia. Loss at 100°, not more than 14%. Ash, not more than 0.5%. **Amylum, U.S.P. X**, is also derived from the grain of *Zea Mays* Linné only, and should contain only a trace of foreign organic matter. Moisture not more than 14% and ash not more than 0.5%. A trituration with 10 parts of water should be neutral to litmus paper and a test for iron is included.

For a gravimetric method for the determination of starch in substance generally, see J. J. Chinay, F. W. Edwards and H. R. Nanji, *Analyst*, 1934, 62.

Details with diagrams, of the microscopical structure of ten common commercial starches.—T. E. Wallis, *Pharm. J.*, ii/1933, 396.

Maranta (B.P.C. '34). Arrowroot is prepared from the rhizomes of *Maranta arundinacea* Linn. Loss at 100°, not more than 20%. Ash, not more than 0.3%.

The government of St. Vincent have defined arrowroot as the separated and purified starch of *Maranta arundinacea*. The starch similar to sweet potato starch with which arrowroot has been adulterated is obtained from "maranta arrowroot," the bulbs of *Myrosma cannifolia*. It is occasionally mixed with arrowroot by the growers.—P. H. Jones, *Food*, 1934, 225.

ANETHUM

Anethum (B.P. '32). Contains not more than 2% of foreign organic matter, and not more than 11% of ash.

The Food and Drug Administration of the U.S. Dept. of Agriculture defines dill seed as the dried fruit of *Anethum graveolens* L. Contains not more than 10% total ash, nor more than 3% ash insoluble in hydrochloric acid.—S.R.A., F.D., No. 2, Rev. 4, Aug. 1933.

Oleum Anethi (B.P. '32). Carvone content not less than 43% and not more than 63% by weight. Determined by the method of the B.P. About 1.5 g. is accurately weighed into a stoppered tube, about 150 mm. long and 25 mm. diameter, 10 ml. of a hydroxylamine reagent (70% of hydrochloride in 900 ml. of 90% alcohol, 4 ml. of dimethyl yellow solution, sufficient N/1 alcoholic potash to produce the full yellow colour of the indicator, and alcohol to 1000 ml.) added, and placed in a water-bath at 75° to 80°; neutralisation of the liberated acid with N/1 alcoholic potash and further heating in the water-bath is continued alternately until the full yellow colour is permanent for 5 minutes heating (about 35 minutes total heating). A duplicate determination is performed using the first titration with an additional 0.5 ml. of N/1 alcoholic potash as colour standard for the titration end-point; from the second titration each millilitre of N/1 alcoholic potash equivalent to 0.1513 (0.1501 × 1.008) g. of carvone. The Pharmacopœia requires the oil to be soluble in an equal volume of alcohol (90%, sp. gr. 0.8334 to 0.8340) and in 10 volumes of alcohol (80%, sp. gr. 0.8634 to 0.8640). Sp. gr., 0.900 to 0.915. Optical rotation, +70° to +80°. Refractive index at 20°, 1.481 to 1.490.

Few oils contain more than 60% of carvone.—*Perfum. essent. Oil Rec.*, ii/1933, 199.

A method of applying the hydroxylamine reaction in the determination of carvone in dill oil.—Bennett and Cocking, *Quart. J. Pharm.*, 1931, 580.

ANISUM

Anisum (B.P.C. '34). The dried ripe fruits of *Pimpinella Anisum* Linn. Contains not more than 2% of other seeds and fruits and not more than 1% of foreign organic matter; acid-insoluble ash, not more than 1.5%. Fructus Anisi, P.G. V yields not less than 1.5% of volatile oil.

The Food and Drug Administration of the U.S. Dept. of Agriculture defines anise, aniseed, as the dried fruit of *Pimpinella anisum* L.; contains not more than 9% total ash or more than 1.5% ash insoluble in hydrochloric acid. Star anise is the dried fruit of *Illicium verum* Hook., and contains not more than 5% total ash.—S.R.A., F.D., No. 2, Rev. 4, Aug. 1933.

Oleum Anisi (B.P. '32). Distilled from Anisum or from the dried fruits of the star anise, *Illicium verum* Hook. f. Should be soluble in 3 volumes of alcohol (90%, sp. gr. 0.8334 to 0.8340), showing not more than a slight opalescence. Sp. gr. (20°/15.5°), 0.980 to 0.994. Optical rotation, -2° to +1°. Refractive index at 20°, 1.553 to 1.560. Freezing-point, not below 15°. M.p., not below 15°.

should comply with a limit for lead. Oleum Anisi, U.S.P. X, may be distilled from the dried ripe fruits of either *Pimpinella Anisum* Linné or *Illicium verum* Hooker filius but the botanical source must be stated on the label. Soluble with not more than a faint opalescence in 3 volumes of 90% alcohol, the similar solution of the recently distilled oil being neutral to litmus paper and developing no blue or brownish colour with 1 drop of ferric chloride solution. Sp. gr. at 25°, 0.978 to 0.988. Refractive index at 20°, 1.5440 to 1.5600.

The lead often contained in this oil is derived from the leaden containers in which most of the oil is imported.

Toxicity of Old Sample of Aniseed Oil. Old oil which can no longer be made to crystallise on cooling shown to be toxic on external application to animals.—Samdahl, *Quart. J. Pharm.*, 1932, 588.

Hydrocarbons of star aniseed oil.—Duncan & Sherwood, *J. Soc. chem. Ind., Lond.*, 1931, 50, 401T; *Quart. J. Pharm.*, 1932, 102.

ANTHEMIS

Anthemis (B.P.C. '34). Dried double or semi-double flower heads of *Anthemis nobilis* Linn. Foreign organic matter, not more than 2%, and acid-insoluble ash, not more than 1%.

Matricaria (B.P.C. '34). Dried flowerheads of *Matricaria chamomilla* Linn. Contains not more than 8% of its stems and other foreign organic matter. Yields not more than 4% of acid-insoluble ash. The N.F. V allows only 5% of stems and other foreign organic matter in Matricaria; the acid-insoluble ash limit is 4%.

Oleum Anthemidis (B.P.C. '34). Soluble in 6 volumes of alcohol (70%, sp. gr., 0.8896 to 0.8901), forming a clear solution. Sp. gr., 0.905 to 0.915. Refractive index at 20°, 1.442 to 1.448. Acid value, 1.5 to 14.0. Saponification value, 260 to 296.

ANTIMONII OXIDUM

Antimonii Oxidum (B.P.C. '34). $\text{Sb}_2\text{O}_3 = 291.5$. As assayed by titration with N/10 iodine of a solution in dilute hydrochloric acid, with the addition of sodium potassium tartrate and a slight excess of sodium bicarbonate, it contains not less than 99% of Sb_2O_3 . Completely soluble when boiled with excess of potassium acid tartrate solution. Antimonii Oxidum, N.F. V, contains not less than 97% of antimonious oxide.

Antimony Poisoning from Enamel. Three outbreaks of poisoning due to drinking lemonade prepared in enamel vessels. Antimony oxide is now used in place of tin oxide as an opacifying agent in the enamelling of hardware, especially of the cheaper types, and these enamels are not acid-proof. In one case as much as 9% of antimony oxide was found in the enamel.—*Brit. med. J.*, i/1933, 423; see also *Lancet*, i/1928, 204, 337.

It might be best for the interests both of the public and the trade if there were total prohibition of antimony in any hollow-ware articles capable of being used for food. The increase in cost of production would be only 3% or 4%.—G. W. Monier-Williams, Min. Health Rept., No. 73, "Antimony in Enamelled Hollow-ware," *Brit. med. J.*, i/1934, 1085.

Acid-Resistance Test for Enamel. The solubility of enamel on enamelled ironware is dependent on the strength of the solutions of organic acids with which it comes in contact. It should be free from antimony, lead, arsenic, and other deleterious or poisonous ingredients. Acid-resistance may be controlled by the following test:—"Enamelware vessels will be considered to be sufficiently resistant to acid if, when filled as full as is convenient with a boiling 0.5% solution of citric acid in water and allowed to stand for 24 hours without being heated or artificially cooled, the amount of ash yielded on ignition of the residue obtained when a definite proportion of the solution is evaporated does not exceed 1.0 mg. per sq. cm. of surface exposed to the action

of the acid, and if on repetition of the treatment with a fresh similar volume of the boiling acid solution not more than a further 0.5 mg. per sq. cm. is obtained. Antimony should be absent from the constituents used in making the enamels. Acid extracts may contain appreciable quantities of borax and significant amounts of fluorine and the exclusion of constituents containing these elements is desirable.—J. H. Coste and D. C. Garratt, *Analyst*, 1935, 215.

The determination of antimony compounds extracted from enamelware by citric acid solution.—R. H. Burns, *Analyst*, 1935, 220.

Fur dermatitis found to be due to presence of antimony 1 in 1000 of the fur. Sweat promotes process of dissociation of the unstable aniline dye compounds with antimony, and sodium chloride may provide the antimony chloride, giving rise to dermatitis. Tartar emetic is a well-known mordant.

A 1 in 1000 solution of antimony tartrate painted on the skin produced rash in 24 hours.—J. Wilson Dougal, *Pharm. J.*, i/1928, 215, 225; *Chem. & Drugg.* i/1928, 354.

Antimony Detection in Biological Liquids. The reagent used is 1 g. of phenazone and 2 g. of potassium iodide in 30 ml. of water. Biological fluids are evaporated and ignited, the residue dissolved in hydrochloric acid and the reagent added; 0.025 mg. of antimony can be detected.—*J. chem. Soc. Abstr.*, ii/1923, 587.

Antimonii Trichloridum, SbCl_3 . In colourless crystals. It is very corrosive and hygroscopic, hence **butter of antimony**, used in veterinary practice, is usually liquid; on addition to water, it decomposes into free hydrochloric acid and basic antimony oxychloride. The anhydrous chloride is used as a catalytic agent in organic reactions. A solution of pure antimony trichloride in chloroform is used as a test for Vitamin A (see Reactions of Vitamin A).

Antimonii et Potassii Tartras (B.P. '32). $\text{C}_4\text{H}_4\text{O}_7\text{SbK}, \frac{1}{2}\text{H}_2\text{O} = 333.9$. Should contain not less than 99% of the pure substance. Assayed by titration of the aqueous solution with N/10 iodine, with the addition of sodium bicarbonate and using starch mucilage as indicator. It is required to comply with a test for alkalinity or acidity by which 1 g. requires for neutralisation to the green colour of bromocresol green indicative of pH 4.5 not more than 2.0 ml. of either N/100 sulphuric acid or N/100 sodium hydroxide. The U.S.P. X allows a purity of 98.5% for Antimonii et Potassii Tartras; the usual limit test for arsenic, after redistilling with stannous chloride as in the B.P. test, is not used for this substance, but is replaced by Bettendorf's test: 0.1 g. in 5 ml. of special concentrated hydrochloric acid on the addition of 10 ml. of special acid stannous chloride (freshly prepared and set aside for 30 minutes) and on comparison with a test omitting the substance under examination, shows no brownish tint or precipitate. *Tartarus stibiatus*, P.G. VI, contains not less than 99.5% of $\text{C}_4\text{H}_4\text{O}_7\text{SbK}, \frac{1}{2}\text{H}_2\text{O}$.

Antimonii et Sodii Tartras (B.P. '32). $\text{C}_4\text{H}_4\text{O}_7\text{SbNa} = 308.8$. Loses not more than 5% of its weight at 100° and then contains not less than 96% of $\text{C}_4\text{H}_4\text{O}_7\text{SbNa}$. The same limit of acidity or alkalinity as for the potassium compound is included and the same method of assay is used. No limit of arsenic is specified.

ORGANIC ANTIMONY COMPOUNDS.

Biological Tests. These substances are tested biologically for toxicity and therapeutic potency in the same way as are the organic arsenicals.

Toxicity Tests. Toxicity tests are usually carried out on mice by injection into the tail vein, and the dose is determined which kills 50% of mice.

Therapeutic Potency. Tests for therapeutic potency may be made as described for neoarsphenamine, but a better method has been described by Gray, Trevan, Bainbridge, and Attwood (*Proc. roy. Soc.*, Ser. B., 1931, 108, 54). Mice are infected with trypanosomes, but a smaller dose of infected material is given than for the neoarsphenamine test. Instead of leaving the mice for two days during which the infection develops unchecked, the agent to be examined is injected at once, ten infected mice each receiving the same dose, and ten other mice each receiving a dose of the substance used as a standard of comparison. No daily examination of the blood of the mice is made, but the number of days each mouse survives is observed. The average period of survival of mice injected with the substance being tested is determined, and also the average period of survival of mice injected with the standard. Should these average survival times not be the same, the experiment is repeated until a dose of the sample is found which gives an average survival time about equal to that given by the chosen dose of the standard.

ARECA

Areca (B.P.C. '34). The dried ripe seeds of *Areca Catechu* Linn. Semen Arecæ, *P.G. VI*, assayed by the process prescribed, contains not less than 0.4% of alkaloid, calculated as arecoline. Semen Arecæ, *P. Helv. V*, contains not less than 0.4% of alkaloids.

P.G. VI Assay. Digest 8 g. of powdered areca with 80 g. of ether, and 4 g. of ammonia solution (9.94% to 10%) and shake the mixture for 10 minutes. After the addition of 10 g. of anhydrous sodium sulphate shake for 5 minutes, pour off the ethereal solution immediately from the mixture, add 0.5 g. of talc, shake for 3 minutes, add 2.5 g. of water and shake. Pour off 50 g. of the dry ethereal solution into a small flask and distil off two-thirds of the ether. Run the cold residue into a separating funnel, rinsing the flask three times with 5 ml. of N/10 hydrochloric acid and 5 ml. of water. After shaking for 3 minutes, let the hydrochloric acid become completely clear, run off into a flask and then repeat the shaking three times in the same manner with 5 ml. of water. Now add to the hydrochloric acid 2 drops of methyl red solution and titrate with N/10 potassium hydroxide until the colour changes. Not more than 3.71 ml. of N/10 potassium hydroxide should be used, since 1.29 ml. of N/10 hydrochloric acid is equivalent to 0.4% of alkaloid. (1 ml. N/10 HCl = 0.015511 g. of alkaloid).

P. Helv. V Assay. The powdered drug is defatted with light petroleum and then extracted with ether; the dried ethereal extract is extracted repeatedly with standard dilute hydrochloric acid and the excess of acid titrated with N/10 sodium hydroxide using methyl red as indicator. Each millilitre of N/10 HCl is equivalent to 0.0155 g. of alkaloid.

Arecolinum hydrobromicum, *P. Helv. V*, contains 99.4% of $C_8H_{13}O_2N \cdot HBr$ and is assayed by titration with N/10 sodium hydroxide. M.p., 169° to 171°.

Methods for the determination of arecoline and other constituents of areca nut.—P. Bourcet, *Brit. chem. Abstr. B.*, 1933, 1035.

ARGENTI NITRAS

Argenti Nitras (B.P. '32). $AgNO_3 = 169.9$. Contains not less than 99.8% of the pure salt. Titrated with N/10 ammonium thiocyanate, using ferric ammonium sulphate as indicator. A limit of copper, bismuth and lead is included. The U.S.P. X also requires a purity of 99.8%.

Argentio Hair Dye (Black or Brown).

No. 1 solution.—Silver nitrate 1, distilled water to 12.

No. 2 solution.—Sulphurated potash 1, distilled water to 8. After washing and drying the hair, the solutions to be applied separately, in above order and after 2 minutes the hair well washed with soft water. This dyes brownish-black with one application, but lighter shades may be obtained by using a weaker strength of No. 1 solution, which should not be allowed to touch the skin.

Pyrogallol Hair Dye (Black).

No. 1 solution.—Pyrogallol 1, alcohol (90%) 8, distilled water 40. Apply before No. 2.

No. 2 solution.—Silver nitrate 1, strong solution of ammonia 1, distilled water to 8. Use in the same manner as the argentic dye.

This dyes grey hair *jet black* with one application.

Various other formulæ for "Silver Hair Dyes"—modifications of the above, e.g., using a small addition of sodium metabisulphite in the No. 1 solution—have been tried producing analogous result, but the difficulty about these preparations is that they simultaneously stain the skin.

Copper Pyro Hair Dyes (Odourless).

LIGHT BROWN.—Cupric chloride ($CuCl_2 + 2H_2O$) and pyrogallol of each 1, water 100.

DARK BROWN.—Cupric chloride 1, ferric chloride 0·5, pyrogallol 1·5, water 100.

BLACK.—Cupric chloride 0·6, ferric chloride 2, pyrogallol 2, water 100. This produces a fairly natural tint.

Iron Tannate Hair Dye (Black). Stated to be non-injurious. After washing the hair and drying it, brush the following thoroughly into the hair: ferrous sulphate 0·6, glycerin 32, water to 500. Repeat the process each day for 3 days. Then with a fine comb apply gallic acid 0·25, tannic acid 0·25, water to 50.—per *Pharm. J.*, i/1926, 5.

Amidol Hair Dye (Black). Amidol 80 grains, sodium sulphite 120 grains, alcohol 10% 1 ounce.

This formula is one of the best *black dyes that will not stain the skin*. The colour develops gradually; any excess of the solution dabbed on can be slightly washed out, leaving the hair dark brown, but to produce a black several applications may be needed. Grey hair so dyed will stand vigorous washing with soap and water without appreciably losing the colour. The hair should be free from grease. The solution deposits the colouring on the side of the bottle. It is odourless and a one-solution dye.

The chemistry of hair dyes.—H. S. Redgrove, *Chem. & Drugg.*, ii/1928, 760.

Argenti Proteinæ (B.P.C. '34). Should contain not less than 7·5% and not more than 8·5% of Ag. Assayed by titration with tenth normal ammonium thiocyanate of the slowly incinerated residue heated with nitric acid till no more coloured fumes are evolved, and diluted. The filtrate from 1 g. shaken with 10 ml. of alcohol should produce no turbidity on the addition of 2 ml. of dilute hydrochloric acid. Argento-Proteinum Forte, U.S.P. X, contains from 7·5% to 8·5% of silver.

Argentum colloïdale, P.G. VI contains not less than 70% of silver and Argentum proteinicum contains at least 8%. Argentum colloïdale, P. Helv. V, contains not less than 70% of silver, and Argentum proteinicum, P. Helv. V, from 8·0% to 8·3%. The silver is converted by careful ignition and subsequent treatment with nitric acid into silver nitrate which is then titrated with ammonium thiocyanate using iron alum as indicator.

Argenti Proteinæ Mite (B.P.C. '34). Assayed by the method for the stronger proteinate, contains from 19·0% to 25·0% of Ag. It complies also with a limit test for silver salts. Argento-proteinum Mite, U.S.P. X, is of the same strength.

ARNICÆ FLOS

Arnicæ Flos (B.P.C. '34). The dried flowerheads of *Arnica montana* Linn. Contains not more than 2% of foreign organic matter, and the percentage of receptacles with their attached involucre is not less than 25 and not more than 33. Yields not less than 15% of alcohol-soluble extractive (45% alcohol) by macerating 5 g. of the air-dried drug, in coarse powder, with 100 ml. of the alcohol for 24 hours, with frequent shaking, filtering and evaporating 25 ml. to dryness and drying at 100°. *Arnica*, N.F. V, should contain not more than 3% of foreign organic matter.

Arnicæ Rhizoma (B.P.C. '34). The dried rhizome and rootlets of *Arnica montana* Linn. Should not contain more than 2% of foreign organic matter. Ash, not more than 12%. Yields not less than 14% of alcohol-soluble extractive (70% alcohol).

ARSENUM

Arseni Triiodidum (B.P. '32). $AsI_3 = 455\cdot7$. As determined by titration with N/10 iodine in presence of sodium bicarbonate, it contains not less than 99·0% of the pure substance. At 100° it

ould not lose iodine, and on volatilisation not more than 0.5% residue remains. Arseni Iodidum, *U.S.P. X*, as determined for halogen content by titration with silver nitrate and potassium thiocyanate, contains not less than 99% of AsI_3 , after drying to constant weight over sulphuric acid.

Arseni Trioxidum (*B.P. '32*). $\text{As}_2\text{O}_3 = 197.9$. Contains not less than 99.8% of As_2O_3 . Residue on volatilisation, not more than 0.1%. Assayed by dissolving in boiling water and N/1 sodium hydroxide, adding an equal quantity of N/1 hydrochloric acid and then sodium bicarbonate, and titrating with N/10 iodine. Arsenious sulphide should be absent as shown by the substance forming a clear colourless solution in 20 parts of dilute solution of ammonia, which does not become yellow when diluted with an equal volume of water and acidified with hydrochloric acid. Arseni Trioxidum, *U.S.P. X*, should contain not less than 99.8% of the pure substance after drying to constant weight at 100° . It is directed that when administered in solid form it must not consist of particles greater than 0.0125 mm. in diameter.

Liquor Arsenicalis. During the preparation nearly half the arsenious oxide combines with the alkali to form meta-arsenite, KAsO_2 , the remainder dissolving uncombined in the meta-arsenite solution. On neutralising with acid the compound is decomposed, the final product consisting simply of a solution of arsenious oxide and potassium chloride.—C. Morton, *Quart. J. Pharm.*, 1933, 4.

Numerous complaints have been made that this preparation is liable to yield a deposit of As_2O_3 crystals and to become fungoid. After thorough investigation M. Smelt (*Quart. J. Pharm.*, 1932, 375) reported that the growth of moulds could be inhibited by adjusting the pH to 2.0 or to 8.0, and the deposition of crystals by adjusting the pH to less than 3.0 or more than 9.0. The paper gives references to the principal previous investigations.

Ferri Arsenas (*B.P.C. '34*). Assayed by titration in diluted sulphuric acid solution with potassium permanganate, it contains not less than 10% of ferrous iron calculated as $\text{Fe}_3(\text{AsO}_4)_2$.

Sodii Arsenas Anhydrosus (*B.P.C. '34*). $\text{Na}_2\text{HAsO}_4 = 185.9$. Loses not more than 2% at 150° and then contains not less than 99.5% of the pure compound. Assayed by interaction with potassium iodide in a 50% hydrochloric acid solution, and titration of the liberated iodine with standard sodium tiosulphate. The crystallised salt of the International Protocol contains 98.85% of arsenic acid. Sodii Arsenas Exsiccatus, *N.F. V*, is required to contain not less than 98% of Na_2HAsO_4 , after drying to constant weight at 150° .

Arsenical Sprays. Lead arsenate is used much for fruit-tree spraying, as is also calcium arsenite. Paris Green, *syn.* Schweinfurth Green, Emerald Green, British Green or French Green, i.e., copper aceto-arsenite, is also used. The sale of arsenical preparations should be limited to registered pharmacists and to persons who obtain a licence for the possession of same.—Sir W. H. Willcox, *Brit. med. J.*, ii/1922, 371.

Lead Arsenate. The specification of the Association of British Insecticide Manufacturers (Bulletin No. 82, Ministry of Agriculture and Fisheries) for lead arsenate (di-plumbic arsenate, PbHAsO_4) requires lead arsenate powder to be in the form of fine powder free from lumps and grit, and to contain not less than 98% of arsenic calculated as arsenic pentoxide, As_2O_5 , not less than 63% of lead oxide (PbO) and not more than 0.5% of water-soluble arsenic expressed as As_2O_5 . A limit test for acidity is also prescribed. Lead arsenate paste consists essentially of a mixture of di-plumbic arsenate and water; it should contain not less than 14% of arsenic (As_2O_5) and not less than 28.4% of lead oxide (PbO). It should comply also with tests for acidity and a limit of 0.5% of water-soluble arsenic.

Arsenical poisoning from apples, it is said, has occurred in consequence of incrustations from fruit sprays, e.g., Bordeaux Mixture and Paris Green.

Of 39 samples of Jonathan, King David and Newtown apples only five were found free from arsenic, and eleven contained more than the statutory limit, and it was found in the flesh of the fruit to the extent of about 3% of that on the peel. Even scrubbing was found to leave appreciable amounts of arsenic on the fruit.—*Brit. med. J.*, i/1926, 297.

Examination of 43 samples of Canadian apples for arsenic showed one-fourth contained less than 1/10,000 grain per lb., and one-third contained

1/10,000 to 1/190 grain per lb. It would be necessary to eat 3 lbs. of raw apple at a time to ingest the minimal medicinal dose of arsenic.—*Lancet*, ii/1926, 8. See also *Analyst*, 1926, 132,291.

Arsenical Weed Killers. The solid form of weed killer is commonly a fine powder, usually coloured, e.g. the "Eureka" weed killer mentioned in the Greenwood case. A sample was found to contain 60% arsenious oxide coloured with phenolphthalein. Accidental poisoning due to liquid weed killer occurred in Sussex in 1919, when a sack of sugar absorbed a quantity of liquid weed killer from a leaking tin placed beside it in transit in a rail carriage. In May 1921, an inquest was held on a woman named Hanktelow at Beckenham. The source of the arsenic appeared to be "Eureka" weed killer.

Arsenic in any shape or form in agriculture and horticulture is uncalled for. For surface-feeding weeds a 5% solution of washing soda in soapy water is quite as destructive as any arsenical weed killer.—A. McCutcheon, *Pharm. J.*, i/1926, 109.

The effect of these enactments (the Protection of Animals Act, 1911, amended in 1927) is to make the use of any poisonous weed killer, in the manner in which weed killers must necessarily be applied, a criminal offence.—Report of the Poisons Board, May, 1935.

Chronic Arsenical Poisoning. An inquiry of the Swedish Commission into chronic arsenical poisoning showed that normal urine might contain quantities of arsenic hitherto associated only with chronic arsenical poisoning. The amounts present in the urine of persons on known diets varied from 0.0 up to 0.58 mg. per litre. Increase of secretion of arsenic traceable to eating fish (especially plaice) which might contain upwards of 3 parts per million, the arsenic appearing in the urine within 24 hours.—*Brit. med. J.*, ii/1924, 932.

Arsenic in shell-fish.—*Lancet*, ii/1926, 1229.

The Llewellyn Case. The deceased was found to have arsenic 0.4 parts per million in the heart and liver and 0.6 p.p.m. in the kidney, but as he had been partial to plaice and other fish this was considered sufficient explanation to account for these traces of arsenic, and a verdict of "Death from Natural Causes" was given.—Sir W. M. Willcox, *Brit. med. J.*, i/1929, 996.

Arsenic poisoning of the whole crew of a French ship (32 men) from drinking wine over a period of 3 months found to contain 12 mg. of arsenic per litre.—per *Lancet*, ii/1932, 690.

Exfoliative dermatitis due to arsenic absorption from wall-paper.—per *J. Amer. med. Ass.*, ii/1929, 1176.

Arsenic eating. 20 grains of coarsely powdered arsenic consumed daily at an arsenic factory. Wishing to give it up, the man promptly had severe gastric pain and diarrhœa; he collapsed and died.—*Brit. med. J.*, ii/1909, 1803.

In Styria, where arsenic is plentiful owing to its production in the smelting of iron ore, there are many arsenic addicts. Nearly every peasant has arsenic in the house. It is used *inter alia* as a "love potion," a remedy for impotence, and to induce abortion. As much as 0.4 g. can be taken by some of these addicts without serious effect.—per *J. Amer. med. Ass.*, ii/1929, 1079.

TESTS FOR ARSENIC

The modified **Gutzeit Test** is used in the *B.P.* '32 and *B.P.C.* '34 with precise directions and a list of limits of arsenic in the substances to be tested given in parts per million.

Marsh's Test consists in generating hydrogen electrolytically or by means of acid and zinc, and adding the substance to be tested. If arsenic be present, arseniuretted hydrogen is evolved, and deposits metallic arsenic in the cooler parts of the delivery tube, which is heated at a suitable point.

The sensitiveness of zinc is invariably increased by the use of cadmium sulphate, and the use of this salt must be regarded as an essential and inseparable feature of the Marsh-Berzelius process.

Estimation of arsenic especially with regard to determination in the tissues. Zinc is unsatisfactory. The arsenic, e.g., in a Marsh, does not appear until the experiment has proceeded for a period of time. The suggestion that there may be deposits or nuclei of arsenic in impure zinc is certainly good. The electrolytic apparatus of Thorpe is preferable to Marsh.—G. Roche Lynch, *Lancet*, ii/1929, 629.

Keratin tissues take up a proportionately greater amount of arsenic than other

issues of the body.—Prof. Sydney Smith, Sect. of Forensic Medicine, B.M.A. Meeting, 1932, *Brit. med. J.*, ii/1932, 320.

Reinsch's Test consists in heating the substance with concentrated hydrochloric acid and copper foil; the arsenic is deposited as arsenide on the foil from which it may be sublimed after washing and drying.

Biological Test. The addition of a substance containing a trace of arsenic to a growing culture of *Penicillium brevicaulis* causes in a few minutes an evolution of arsine which can be detected by the smell. 0.0000001 g. of As can be detected.—B. Gosio, *Boll. Ist. sieroter. Milano*, 1932, 61, 597.

The gas evolved is trimethylarsine.—F. Challenger et al., *J. chem. Soc.*, 1933, 95.

ORGANIC ARSENIC COMPOUNDS

Acetarsol (*B.P.C.* '34). $C_8H_{10}O_5NaAs = 275.0$. It may be assayed by the process of the British Pharmaceutical Codex in which a solution of the substance in water with a few drops of N/1 sodium hydroxide is boiled with ammonium persulphate until colourless; 2N oxalic acid is added and boiled until carbon dioxide is no longer evolved, then 2N sulphuric acid and potassium iodide are added and the solution boiled until it is a pale straw colour; after decolorisation with a few drops of sodium thiosulphate, dilution with water, addition of 2N sodium carbonate and an excess of sodium bicarbonate, it is titrated with N/10 iodine using starch mucilage as indicator; it should contain not less than 27.0% and not more than 27.4% of As. Complies with a test for limit of free amino-acid. (For further information on this compound see Volume I, page 186, under Stovarsol.)

Arsphenamina (*B.P.C.* '34). Complies with biological tests, carried out in an approved institution or laboratory, for maximum toxicity and therapeutic potency (*vide infra*) and contains, when determined by an approved method, from 30% to 34% of As. It is controlled by regulations made under the Therapeutic Substances Act, 1925, the standard preparation for Great Britain and Northern Ireland being kept in the National Institute for Medical Research, London. It is not included in the *B.P.* '32 because it is now very little used. The percentage of As may be determined by the *B.P.C.* method for Sodii Aminarsonas. When kept in sealed phials at a temperature of 56° for twenty-four hours, it retains its colour, physical properties and solubility. It should comply with tests for solubility in water, a sodium hydroxide solution and a sodium chloride solution. Arsphenamine, *U.S.P. X*, complies with the requirements of the United States Public Health Service and contains not less than 30% of arsenic. Assayed by digesting for ten minutes with five times its weight of powdered potassium permanganate and 25 volumes of diluted sulphuric acid, mixing well, a further 10 volumes of concentrated sulphuric acid is then added in small portions, the brown precipitate dissolved with just sufficient hydrogen peroxide, diluted and boiled to expel the excess; sufficient potassium permanganate is added to produce a pink coloration, this being decolorised with a drop of N/10 oxalic acid; the cooled solution is then set aside in the dark for one hour with potassium iodide when the liberated iodine is titrated with N/10 thiosulphate; a blank titration is made.

Salvarsan, neosalvarsan, salvarsan-sodium, silver-salvarsan, neosilver-salvarsan and sulphoxyl-salvarsan are official in the *P.G. VI*.

Quantitative methods for the determination of arsenic in organic arsenical compounds are also described in Methods of Analysis (*A.O.A.C.*, 1930, 479).

Tests for Arsphenamine: Recognition in Medico-Legal Cases. The behaviour of arsphenamine with the usual reagents for arsenic has been investigated to find a method of distinguishing between it and inorganic arsenic in medico-legal cases.

Muscle from a patient who had died three weeks after injections of arsphenamine still gave reactions for arsenic. The drug gives the Reinsch, Marsh, Gutzeit (after oxidising and reducing) and biological tests for arsenic. The following serve to distinguish arsphenamine from inorganic forms of arsenic. With Bettendorf's reagent it gives an amorphous, yellow ppt. which dissolves on warming and reappears on cooling. H_2S gives no ppt. even after a solution of the drug has been boiled with HCl. The organic part of the arsphenamine molecule gives certain reactions, which may afford confirmatory evidence of the presence of the drug, thus:—The corresponding diazo-derivative gives a characteristic red to violet precipitate with α -naphthylamine, which may be isolated and examined for arsenic by the Reinsch or Gutzeit test. Sodium aminar-

sonate behaves similarly, giving a red azo-dye, but the diazotised arspnenamine gives no colour with β -naphthylamine, whilst sodium arminarsonate gives vermilion-red azo colouring matter with the β -amine.

Minced horseflesh sprayed with arspnenamine solution and kept for 14 days was extracted with alcohol, slightly acidified with HCl. The residue so obtained gave positive results with the Reinsch, Gutzeit, and α -naphthylamine tests but negative results with Bettendorf's reagent, and with hydrogen sulphide. So far it has proved impossible to obtain good results by applying to arspnenamine ordinary toxicological methods for the estimation of arsenic, the latter being obtained only to the extent of from 29% to 29.5% out of the 34% present.—*J. chem. Soc. Abstr.*, ii/1911, 448. See also Sir W. H. Willcox *Brit. med. J.*, i/1916, 474.

Estimation of the **arsenic excreted in the urine** has been conducted, the general conclusions being: (a) the elimination begins rapidly; (b) the duration of the passing of arsenic in the urine is longer than was thought; (c) after *subcutaneous* injection the elimination is concluded more rapidly than by the intramuscular method; (d) simultaneous use of mercury caused delay in eliminating the arsenic; (e) potassium iodide given at the same time shortens the duration of the arsenic elimination.

It appears the excretion is much slower with salvarsan than with Atoxyl or Arsacetin when injected subcutaneously; also that whilst Atoxyl and Arsacetin are excreted quickly and almost completely by the urine, in the case of "606" the arsenic is largely to be found in the fæces.

After hypodermic, gastric or intramuscular use the elimination of arsenic in the urine lasts about 25 days. The arsenic, it is said, is largely changed in the ionic condition, and this may be related to its antisyphilitic action.—*J. chem. Soc. Abstr.*, ii/1912, 968.

For references to untoward results see Vol. I.

Biological Tests.

Arsphenamine must be tested for toxicity and therapeutic activity. The Regulations under the Therapeutic Substances Act, 1925, do not give directions for these tests, but the directions are supplied on application to the Ministry of Health. The directions describe the tests carried out in the National Institute for Medical Research, London.

(a) **Toxicity Test.** This is carried out on mice of uniform weight. 0.1 g. arspnenamine is weighed and dissolved in about 6 ml. of water. The water is freshly distilled, being condensed and collected in glass vessels. 0.45 ml. 2N sodium hydroxide is added, the liquid shaken and diluted to 10 ml. With this 1% solution five mice are injected with a dose corresponding to 0.1 mg. per g. and five mice with a dose of 0.125 mg. per g. The injections are made into the tail vein. The mice are observed during 3 days. The sample is regarded as non-toxic provided that at least three mice out of five have survived each dose.

(b) **Test for Therapeutic Potency.** The curative action of each sample is tested on mice infected with a species of trypanosome. *Trypanosoma equiperdum* is commonly used because it is non-pathogenic to man. This strain of trypanosome is carried for long periods in guinea-pigs and is transferred to rats by injecting some of the guinea-pigs' blood into the peritoneal cavity. When the test is to be carried out some thirty mice are infected from the blood of an infected rat. The trypanosomes in the rat's blood are counted and each mouse receives 0.5 ml. of a suspension containing a certain number of organisms. After 2 days the trypanosomes in the blood of each mouse are counted. The hæmocytometer apparatus for counting red blood cells is used, the trypanosomes being stained with methyl violet. Those mice are used for the test which contain in their blood not less than 100,000 and not more than 500,000 trypanosomes per cu. mm. of blood. At least ten mice are then injected by way of the tail vein with the sample being tested, a dose of 0.01 mg. per g. being given; at least ten mice are also injected with the standard sample of arspnenamine at the same dose. The blood of the mice is then examined daily for the next few days to discover the rate of disappearance of trypanosomes. A sample is only accepted as satisfactory if its curative action is at least as quick as that of the standard and is seen in as large a proportion of mice.

Arsphenamina Argentica (B.P.C. '34). Controlled by regulations made under the Therapeutic Substances Act and complies with biological tests carried out in an institution or laboratory approved by the licensing authority.

for maximum toxicity and therapeutic potency (*vide infra*). By an approved method, such as that given under Sodii Aminarsonas, it contains not less than 18% and not more than 21% of As; it contains not less than 12% and not more than 13% of Ag, estimated by an approved method. The 5% aqueous solution should be almost black, and alkaline to litmus, and on the addition of sodium hydroxide or sodium carbonate no precipitate is produced, but with sodium bicarbonate a precipitate appears. It may be assayed for Ag by adding ammonium persulphate to an aqueous solution and boiling until colourless, diluting, adding nitric acid and titrating with N/50 ammonium thiocyanate to ferric ammonium sulphate indicator.

For the toxicity test, doses corresponding to 0.125 mg. and to 0.15 mg. per g. body weight are injected in 1% solution into the tail vein of each of five mice. Three mice must survive each dose. For the therapeutic test a 0.05% solution is injected into infected mice. Five receive 0.009 mg. per g. body weight and five receive 0.008 mg. The tests are performed as for arsphenamine.

Neoarsphenamina (*B.P.* '32). Controlled by regulations made under the Therapeutic Substances Act and complies with biological tests, carried out in an approved institution or laboratory, for maximum toxicity and therapeutic potency (*vide infra*). The standard preparation of neoarsphenamine is kept in the National Institute for Medical Research, London. It complies with a test for solubility, and absence of arsphenamine. Kept in sealed phials for 24 hours at 56° it retains its colour, physical properties and solubility. Neoarsphenamina, *U.S.P. X*, complies with the requirements of the United States Public Health Service and should contain not less than 19% of As, determined by the *U.S.P. X* process for Arsphenamine.

The *B.P.* standard for the As content should have been the same as that included in the Regulations under the Therapeutic Substances Act, namely 18% to 21%.—*Pharm. J.*, ii/1932, 129.

Biological Tests.

Neoarsphenamine is tested for toxicity and potency by tests similar to those given for arsphenamine.

(a) **Toxicity test.** An important study of the toxicity of neoarsphenamine has been published by Durham, Gaddum and Marchal (1929, *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 128). They determined the curve relating the percentage of mice killed to the dose injected, obtaining a curve for mice of 14 g. and also for mice of 19 g. The dose of the international standard neoarsphenamine which kills 50% of mice of 14 g. weight is 8.1 mg. By international agreement samples are allowed to pass the test if they do not exceed the toxicity of the standard by more than 20%, hence it would be expected that the dose of a sample to be injected would be $\frac{5}{6} \times 8.1$ or 6.75 mg. Actually the requirement in Gt.

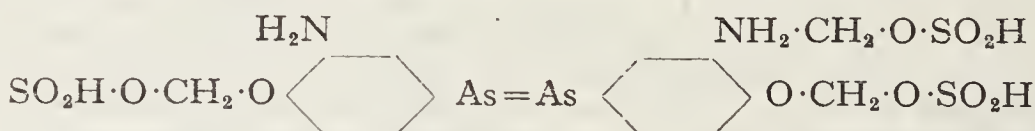
Britain is more lenient than this, for the dose to be injected is only 6 mg., from which it follows that samples exceeding the toxicity of the standard by 35% are accepted. Apparently no country imposes a more severe standard than this despite the international agreement to do so. The test requires a dose of 6 mg. in 2% solution to kill not more than 15 out of 30 mice of 13 to 15 g. weight. Experience has shown that some samples which pass this test are more toxic when injected in stronger solution, and therefore a subsidiary test in which a 5% solution is used is also performed. A dose equivalent to 0.225 mg. per g. is injected into five rats, of which not more than one may die if the sample is to be approved.

(b) **Therapeutic test.** The test is similar to that for arsphenamine. Five infected mice receive 0.03 mg. per g. as a 0.2% solution, and 5 mice receive 0.025 mg. per g. Similar doses of the standard are also given to the same number of other mice.

Variations in Toxicity and Trypanocidal and Spirochæticidal Properties. 18 samples, prepared by 7 different laboratories, of neoarsphenamine purchased on the open market were found to vary considerably. The maximum tolerated dose for white rats varied from 0.200 g. to 0.300 g. per kilo of weight; the average minimal trypanocidal dose varied from 0.004 to 0.008 g. per kilo weight, 28% being incompletely trypanocidal; and with the average minimal spirochæticidal dose for rabbits with acute syphilitic orchitis of 0.020 g. per kilo, 14 samples were completely spirochæticidal in this dose while 6 were not. The establishment of standards urged.—J. F. Schomberg and J. A. Kolmer, *J. Amer. med. Ass.*, i/1933, 183.

Sulpharsphenamina (*B.P.* '32). Controlled by the regulations made under the Therapeutic Substances Act, 1925. The standard preparation is kept in the National Institute for Medical Research, London. It complies with biological tests, carried out in an institution or laboratory approved by the licensing authority, for maximum toxicity and therapeutic potency (*vide infra*). It should comply with a test for absence of arsphenamine, and should retain its colour, physical properties and solubility when kept in sealed phials at 56° for 24 hours.

Constitution. The constitution given in the *B.P.* is not correct. It appears to be a sodium salt of 3 : 3' -diamino-4 : 4'-dihydroxyarsenobenzene-OO'N-trimethylenesulphurous acid.—



in which a methylenesulphite group is attached to a phenolic group.—W. J. C. Dyke and H. King, *J. chem. Soc.*, 1933, 1003.

The biological tests for sulpharsphenamine are similar to those for neoarsphenamine except that the doses are given by subcutaneous injection. For the toxicity test on mice, the volume injected into each mouse of 14 g. is 0.35 ml. of a 2% solution; for the subsidiary test on rats each rat receives 0.35 mg. per g. in 10% solution. For the therapeutic test, five mice receive 0.05 mg. per g. and five mice receive 0.04 mg. per g., both given as a 0.2% solution.

Sodii Aminarsonas (*B.P.C.* '34). $\text{C}_6\text{H}_7\text{O}_3\text{NAsNa} = 239.0$. Contains from 24% to 25.6% of As, when assayed by the method of the *B.P.C.* '34: 0.2 g., accurately weighed, is heated for 1 hour with 5.5 ml. of sulphuric acid and 1 ml. of fuming nitric acid; to the slightly cooled product 15 drops of fuming nitric acid are added and heat applied for a further 5 minutes; 1 g. of ammonium sulphate is cautiously added and after cessation of evolution of nitrogen, cooling, and diluting to about 70 ml., 1 g. of potassium iodide is added and the liquid concentrated to about 40 ml.; after decolorisation with just sufficient N/100 sodium thiosulphate and dilution to about 110 ml., the addition of 50 ml. of 4N sodium carbonate and a slight excess of sodium bicarbonate, for neutralisation, the mixture is titrated with N/10 iodine, using starch mucilage as indicator.

Sodii Cacodylas (*B.P.C.* '34). $\text{C}_2\text{H}_6\text{O}_2\text{AsNa}, 3\text{H}_2\text{O} = 214.0$. By the *B.P.C.* method for Sodii Aminarsonas it contains from 72% to 75% of $\text{C}_2\text{H}_6\text{O}_2\text{AsNa}$. It complies with limits for acidity or alkalinity to phenolphthalein, disodium methyl arsonate, arsenate and phosphate. The *U.S.P. X* allows the same limits for the anhydrous substance, assayed, after neutralisation to phenolphthalein, by titration with N/1 hydrochloric acid to methyl orange. Natrium kakodylicum, *P.G. VI*, $(\text{CH}_3)_2\text{AsO}_2\text{Na} + 3\text{H}_2\text{O}$, contains 32.8% to 35% of arsenic.

Tryparsonum (*B.P.C.* '34). $\text{C}_8\text{H}_{10}\text{O}_4\text{N}_2\text{AsNa}, \frac{1}{2}\text{H}_2\text{O} = 305.0$. Tryparsone contains from 25.1% to 25.5% of arsenic, and from 9.25% to 9.5% of nitrogen, calculated on the substance dried at 105° to 110°, at which temperature the loss is not less than 2.5% and not more than 3.5%. Should comply with tests for absence of soluble inorganic arsenates and for absence of arsanilic acid. A dose equivalent to 0.75 g. per kilo of body weight produces no toxic symptoms when injected intravenously into a rabbit. Assayed for arsenic by heating with sulphuric and fuming nitric acids, addition of ammonium sulphate and potassium iodide, boiling, decolorisation with sodium thiosulphate, addition of sodium carbonate and sodium bicarbonate, and titration with standard iodine. Assayed for nitrogen by the Kjeldahl method, distilling the ammonia formed into excess of standard acid, and back titrating with sodium hydroxide using methyl red as indicator.

For information concerning the composition and uses of this important compound, see *Tryparsamide* (Vol. I, page 188).

Trypanocidal action and chemical constitution of arsenic compounds.—H. King, W. O. Murch and I. E. Balaban, *J. chem. Soc.*, 1925, 2632, 2701.

AZORUBRUM

(and Other Medicinal Dyes)

Azorubrum (*B.P.C.* '34). $\text{C}_{20}\text{H}_{12}\text{N}_2\text{O}_7\text{S}_2\text{Na}_2 = 502.2$. (Bordeaux B—Colour Index No. 88). Sulphated ash, not more than

65%, of which that from 1 g. dissolved in 20 ml. of water and 2 ml. of dilute hydrochloric acid, produces no precipitate of zinc ferrocyanide upon the addition of 1 ml. of potassium ferrocyanide solution. Bordeaux B is practically unaffected by dilute acids or alkalis or by exposure to sunlight, but in use it must not be confused with other dyes known by the same name.

Magenta (B.P.C. '34) (Colour Index No. 677). The sulphated ash is not more than 5% and that from 1 g. gives no precipitate of zinc ferrocyanide. This is basic fuchsine and should be distinguished from acid fuchsine (Colour Index No. 692).

Carminum (B.P.C. '34). Loses not more than 15% of its weight at 100°, and then yields not more than 10% of ash. A limit of insoluble matter is included.

Methylthioninæ Chloridum (B.P. '32). $C_{16}H_{18}N_3ClS = 319.7$. Methylene blue is assayed by titration, in boiling aqueous solution acidified with hydrochloric acid, the air in the flask being replaced by carbon dioxide, with N/10 titanous chloride until the blue colour is replaced by a reddish-grey; 1 ml. of N/10 titanous chloride is equivalent to 0.01598 g. of $C_{16}H_{18}N_3ClS$, and a purity of not less than 80% is indicated. The solution on reduction is decolorised with potassium iodide, it produces a deep blue flocculent precipitate, with a pale blue supernatant liquid, and, on oxidation with potassium dichromate, gives a reddish-violet colour and a bluish-violet precipitate, the blue colour being restored with sulphurous acid. A limit of zinc is included. Methylthioninæ Chloridum, U.S.P. X, is the trihydrate ($C_{16}H_{18}N_3ClS \cdot 3H_2O$) and loses not more than 16% at 110°; ash, not more than 1%; a limit of dextrin, insoluble in boiling alcohol and dried at 100°, corresponds to not more than 1%.

In the absence of B.P. limits for moisture and ash, 20% of the material may be neither water nor methylene blue.—*Pharm. J.*, ii/1932, 126.

An official quantitative method for the determination of methylthionine chloride in tablets and capsules is described in Methods of Analysis (A.O.A.C., 1930, 456.)

Medicinal methylene blue is preferable to the commercial for making alcoholic solutions for bacteriological staining, as being more soluble, cf. Löffler's alkaline methylene blue.

For the use of methylene blue as a renal function test, see p. 331.

Methylviola (B.P.C. '34) (Colour Index No. 680). Methyl violet yields not more than 5% of sulphated ash, of which that from 1 g. gives no precipitate of zinc ferrocyanide in presence of hydrochloric acid. Limit of dextrin insoluble in boiling alcohol, not more than 1%.

Novaurantia (B.P.C. '34). $C_{16}H_{10}N_2O_7S_2Na_2 = 452.2$. (Colour Index No. 27). Orange G yields not less than 36% and not more than 50% of sulphated ash. The sulphated ash from 1 g. gives no precipitate of zinc ferrocyanide.

Rubrum Scarlatinum (B.P.C. '34). (Colour Index No. 258). Scarlet red yields not more than 10% of sulphated ash.

Tartrazina (B.P.C. '34). $C_{16}H_9O_9N_4S_2Na_3 = 534.2$. (Colour Index No. 640). Leaves not more than 80% of sulphated ash, which complies with the limit test for zinc.

Viola Crystallina (B.P.C. '34). (Colour Index No. 681). Crystal violet yields not more than 5% of sulphated ash, which should comply with the limit test for zinc.

Viride Malachitum (B.P.C. '34). (Colour Index No. 657). Malachite green yields not more than 1% of sulphated ash, which should comply with the limit test for zinc.

Viride Nitens (B.P.C. '34). (Colour Index No. 662). $C_{27}H_{33}N_2SO_4H = 482.3$. Brilliant green yields not more than 5% of sulphated ash which complies with the limit test for zinc.

Indicarminum (B.P. '32). $C_{16}H_8O_8N_2S_2Na_2 = 466.2$. Indigo carmine is assayed by titration with N/10 potassium permanganate in warm solution acidified with an equal volume of dilute sulphuric acid, the colour changing from green to pale yellow; each ml. of N/10 potassium permanganate is equivalent to 0.0133 g. of $C_{16}H_8O_8N_2S_2Na_2$ of which not less than 90% should be indicated, calculated on the substance dried at 100°. Loss at 100°, not more

than 10%, and the residue on ignition and re-ignition with sulphuric acid is then not less than 30% and not more than 40%. *Sodii Indigotindisulphonas*, U.S.P. X, after drying at 100°, leaves not more than 2% of residue insoluble in water. Tests for starch or starch iodide and iron ferricyanide or ferrocyanide are included.

For the use of indigo-carmin as a renal function test see p. 330.

Indigo or Indigotin (natural) is obtained from the shoots of *Indigofera tinctoria* (Leguminosæ) in India and Java, by maceration with lime and water. The pure substance has the composition $C_{16}H_{10}N_2O_2$.

Indigo Soluble as mostly understood is the acid substance not the sodium salt.

Isatin. $C_8H_5NO_2$. Yellowish-red prismatic crystals obtainable by oxidising indigo with chromic or nitric acid, also by boiling *o*-nitrophenylpropionic acid with caustic soda.

Litmus, syn. Lackmus (German), is a blue pigment obtained from *Rocella tinctoria* (Discomycetes). Employed chiefly as an indicator for acid and alkali as Litmus Paper, also in form of solution in volumetric analysis. Litmus is made in Holland by fermenting lichens in presence of ammoniacal liquids and potash.

LITMUS SOLUTION (see Indicators, p. 221).

In titration, all CO_2 must be removed by boiling before taking end reaction. Not suitable for weak bases. Quinine, morphine and strychnine are neutral to it and the acids in their salts can be titrated as if base were absent.

Carbon dioxide only turns litmus "wine red" when alkaline bicarbonates are present as impurities, otherwise it turns it red just like any other acid.

LACMOID, also known as Resorcin Blue, is chiefly diazo-resorcin. Solution (0.2% in dilute alcohol), employed as indicator, closely resembles litmus in reactions.

Cudbear, syn. Red Indigo, a purplish-red powder obtained by the ammoniacal fermentation of *Lecanora tartarea* and other lichens, designated in Germany *Persio*, in France *Orseille de terre*. Except for the fact that it is in the condition of a fine powder it is virtually the same as orchil.

Archil, syn. Orchil. The word Archil, or more properly Orchil, was originally the name of the plant from which the dye, which goes under this name, is obtained. It appears that before the introduction of orchil into this country a similar dye obtained from certain lichens in Scotland was in use under the name "Cork." This is given in Miller's "Plant Names" as the name of the lichens yielding archil.

It is made from various lichens, e.g., *Rocella*, *Lecanora*, etc. The lichens are ground up and fermented with addition of stale urine or ammonia. Its production is similar to that of litmus except that the potash is omitted. In commerce it is usually in the form of a pasty mass known as archil (French, *Orseille en pâte*).

Turnsole, syn. Tournesol (French). The familiar colouring used on Dutch cheeses. The word has been more particularly applied to a product from *Chrozophora tinctoria* A. Juss (*Croton tinctorius* Linn.)—a native of Southern Europe and the Orient. Rags soaked in the juice of this plant are exported to Holland. They change colour on exposure to ammonia vapour, and this purple colour can be extracted with water for the purpose in question. Turnsole was at one time supposed to form the colouring matter of litmus.

BALSAMUM PERUVIANUM

Balsamum Peruvianum (B.P. '32). Balsamic esters, determined by extraction with ether in alkaline solution, evaporation and drying at 100° for 30 minutes, not less than 53% and having a saponification value of not less than 235. Balsamum Peruvianum, U.S.P. X, by a similar but aliquot part method, yields 50% to 60% by weight of cinnamein, having a saponification value of 235 to 238; acid number, 56 to 84.

It would be wiser to include a lower minimum limit for balsamic esters.—A. D. Powell, *Quart. J. Pharm.*, 1932, 554.

Various qualitative tests for the detection of adulteration are described.—E. M. Smelt, *Quart. J. Pharm.*, 1932, 378.

Balsamum Tolutanum (B.P.'32). Free balsamic acid content, 19 % to 25 %, and total balsamic acid content, 35 % to 50 %, both calculated with reference to the dried alcohol-soluble matter. Assayed by precipitation, for free balsamic acids in an alcoholic potash solution and total balsamic acids in a saponified solution, with magnesium sulphate, filtration and extraction of the acidified filtrate with ether, transferring to sodium bicarbonate solution, re-extraction with ether and drying in a vacuum desiccator over sulphuric acid. Acid value, by a specified process, 97 to 160; ester value, 47 to 95; saponification value, 170 to 224—all calculated on the dry alcohol-soluble matter. Matter insoluble in alcohol, not more than 4 %. Loss *in vacuo* over sulphuric acid, not more than 4 %. Tolu, *U.S.P. X*, has an acid number of 112 to 168 and a saponification value of 154 to 220.

Benzoinum (B.P. '32). Sumatra benzoin only is official. The dry alcohol-soluble matter yields from 19 % to 29 % of free balsamic acids, and 30 % to 60 % of total balsamic acids, and has an acid value of 115 to 163, an ester value of 47 to 83, and a saponification value of 169 to 223. Alcohol-insoluble residue, dried at 100°, not more than 20 %. Loss *in vacuo* over sulphuric acid, not more than 10 %. Ash, not more than 2 %. The *U.S.P. X* requires Sumatra benzoin to yield 75 % of alcohol-soluble extractive and not more than 1 % of acid-insoluble ash, and Siam benzoin, not more than 1 % of foreign organic matter, 90 % of extractive, and not more than 0.5 % of acid-insoluble ash.

The *B.P.* ash limit is too stringent and the acid and ester values will exclude many genuine samples.—E. J. Parry, *Chem. & Drugg.*, ii/1932, 251.

Styrax (B.P. '32). Loses in one hour on a water-bath not more than 5 % of its weight and then contains not less than 30 % of total balsamic acids, has an acid value of 55 to 90, an ester value of 100 to 133, and a saponification value of 170 to 200. Styrax, *U.S.P. X*, is not the purified product and both the Levant and American varieties are official. After purification it has an acid value of 56 to 85 (Levant storax) or 38 to 85 (American storax), a saponification value of 160 to 200, and yields not less than 25 % of cinnamic acid.

Copaiba (B.P. '32). Residue, when heated on a water-bath, 50 % to 65 %. Sp. gr., 0.960 to 0.995. Acid value, calculated on the non-volatile residue, 120 to 160. Optical rotation of the distilled oil, -7° to -35° . Copaiba, *U.S.P. X*, has sp. gr. 0.940 to 0.995 at 25° and an acid value of the original balsam of 28 to 95; the residue insoluble in absolute alcohol and dried at 80° should not be more than 5 %; the volatile oil, obtained by steam distillation, should not boil below 250° and in a 10 decimeter tube should show an angular rotation of not less than -5° at 25°.

Oleum Copaibæ (B.P.C. '34). Sp. gr., 0.895 to 0.908. Optical rotation, -7° to -35° . Refractive index at 20°, 1.495 to 1.500.

Terebinthina Canadensis. The balsam obtained from *Abies balsamea* Mill (Pinaceæ), known as Canada balsam. It has a refractive index approximating that of microscopic glass, and "sets" in a non-crystalline transparent condition, hence is used as a mounting medium. In preparing for use it has to be gently heated in an open dish for a week or more until a small quantity removed becomes brittle when placed on a cold slab. Canada balsam 1 part by weight in xylol, in turpentine, in benzol, and in chloroform, each 1 by measure, are prepared for microscopic use. The first mentioned is chiefly employed and is frequently designated "Xylol-Balsam."

BARBITONUM

Barbitonum (B.P. '32). $C_8H_{12}O_3N_2 = 184.1$. M.p., 189° to 192°. Ash not more than 0.05 %. Neutral and basic substances, not more than 0.1 %. Barbitalum; *U.S.P. X*, yields not more than a negligible ash from 0.5 g.

Barbitonum Solubile (B.P. '32). $C_8H_{11}O_3N_2Na = 206.1$. Yields, by extraction with ether from acidified solution and drying at 100°, barbitone equivalent to not less than 97 % of the pure sodium salt. The *U.S.P. X* requires Barbitalum Solubile to lose not more than 1 % at 100°, and then yield 88 % to 90 % of barbitone, which leaves a negligible ash.

Phenobarbitonum (B.P. '32). $C_{12}H_{12}O_3N_2 = 232.1$. M.p., 173° to 177° . Ash, not more than 0.05%. Phenobarbitalum, U.S.P. X, leaves a negligible ash.

Phenobarbitonum Solubile (B.P. '32). $C_{12}H_{11}O_3N_2Na = 254.1$. Contains not less than 95% of the pure substance.

Allobarbitonum (B.P.C. '34). $C_{10}H_{12}O_3N_2 = 208.1$. M.p., 171° to 172° . Ash, not more than 0.1%.

An official quantitative method for the determination of barbitone or phenobarbitone in tablets is described in Methods of Analysis (A.O.A.C., 1930, 484).

Extraction and Identification of Barbiturates in Urine. To 500 ml. of sample add 50 ml. of 15% potassium ferrocyanide solution. Shake and add 50 ml. of a solution of zinc acetate containing 112 g. per 100 ml. Again shake, filter and acidify filtrate if necessary with acetic acid. Extract the filtrate with 5 successive portions of 75 ml. of ether, dry the ethereal extracts over anhydrous sodium sulphate and distil off the ether. Extract the residue with 20 ml. of boiling alcohol, filter into a tared dish and evaporate to dryness. If the residue is white, it is weighed; if not white, dissolve in water, decolorise with charcoal and again evaporate and weigh. The barbiturate is then best identified by Denigés' microchemical method.—Paget and Desodt, *J. Pharm. Chim.*, 1933, 207.

Microchemical Detection of Barbituric Acid Compounds. The reactions of the following barbituric acid compounds are described in tabular form, and illustrated by drawings of the various types of crystals formed: Veronal (diethylbarbituric acid, m.p. 191°), proponal (dipropylbarbituric acid, m.p. 145°), dial (diallylbarbituric acid, m.p. 170° to 171°), allonal (allylisopropylbarbituric acid, m.p. 141.5°), soneryl (butylethylbarbituric acid, m.p. 123°), luminal (phenylethylbarbituric acid, m.p. 174° to 176°), rutonal (phenylmethylbarbituric acid, m.p. 226° to 228°), phanodorm (cyclohexenylethylbarbituric acid m.p. 173°), and sandoptal (isobutylallylbarbituric acid, m.p. 138° to 139°). When the 2% solutions of the compounds in potassium hydroxide are precipitated with nitric acid, proponal, dial, luminal and rutonal form well-defined crystals at once, but veronal, allonal, soneryl, phanodorm and sandoptal give a finely divided amorphous precipitate, slowly becoming crystalline. On adding ammonium phosphate or other ammonium salt to the 2% solutions in potassium hydroxide, veronal, proponal, dial, luminal, rutonal and sandoptal give at once well-formed cubic and rhombic crystals, whilst after some time, allonal, soneryl and phanodorm form crystals belonging to the binary system.

Reaction with thallium acetate. When the 2% potassium hydroxide solutions are treated with thallium acetate, only veronal, proponal, allonal and phanodorm give crystalline compounds. **Reaction with silver nitrate.** When the compounds are treated with 5% ammoniacal silver nitrate all but veronal and dial give soluble silver compounds. **Reaction with ammoniacal cuprous solution.** To the 2% potassium hydroxide solutions copper acetate is added and enough ammonia to dissolve the hydroxide precipitated. The reaction goes even better when Schweitzer's reagent is used instead. The copper ammonia compounds are all soluble except those of dial, rutonal and sandoptal, which give amethyst-coloured crystals. **Reaction with bromine water.** All the compounds except veronal give an amorphous precipitate with bromine water from the 2% solution in potassium hydroxide; with proponal, luminal, rutonal and phanadorm this slowly becomes crystalline. **Reaction with baryta water.** Only dial gives crystals. From the above reactions it is possible to identify any of the given barbituric acid compounds.—L. van Itallie and A. J. Steenhauer, *Pharm. Weekbl.*, 1930, 977.

BATTISTA

Battista (B.P.C. '34). With boiling water, or when heated with steam, battiste must show no stickiness or deterioration. Weight per square yard not less than 5 oz., of the fabric alone not less than 2 oz., and the difference of these not less than 3 oz. Average threads per inch, not less than 104 in the warp and 72 in the weft.

Jaconettum (B.P.C. '34). With boiling water or when heated with steam jaconet must show no stickiness or deterioration. Weights per square yard not

less than 6 oz. total, fabric alone 2 oz., and the difference 4 oz. Not less than average number of 104 threads in the warp and 72 threads in the weft per inch.

Sericum Oleatum (B.P.C. '34). Oiled silk—minimum weights per square yard for oiled fabric 2.5 oz., and for silk fabric alone 0.33 oz. Average number of threads per inch, not less than 120 in the warp and 85 in the weft.

Sindon Oleata (B.P.C. '34). Oiled cambric—minimum weights per square yard for the oiled fabric 4 oz., for cotton fabric alone 1.5 oz., and the difference 2.5 oz. Average number of threads per inch, not less than 74 in the warp and 68 in the weft.

BELLADONNA

Belladonnæ Folium (B.P. '32). Should comply with the following standards: foreign organic matter, not more than 2%; stem, not more than 20%; stems greater in width than 5 mm., not more than 1%; ash, not more than 15%; acid-insoluble ash, not more than 3%. By extraction with an ammoniacal ether alcohol mixture (4 : 1), transferring to acid, extraction of the liberated alkaloids with chloroform, evaporation of the solvent, and drying for 30 minutes at 100°, it gives a titration with N/50 sulphuric acid equivalent to not less than 0.3% of alkaloids calculated as hyoscyamine. *Belladonnæ Folia, U.S.P. X*, is assayed by extraction with ether-chloroform (3 : 1), finally evaporating the alkaloid with alcohol or ether and titrating without heating at 100°; it should yield not less than 0.3% of alkaloids and not more than 3% of acid-insoluble ash, and contain not more than 3% of stems over 10 mm. in diameter. *Folia Belladonnæ, P.G. VI*, yields not less than 0.3% of hyoscyamine.

Experiments by A. F. Sievers at the Office of Drug Plant Investigation, Washington, on *Atropa Belladonna* (first, second, and third year's growths) showed that the alkaloidal content of the leaves of first year's plants (1910) gave an average of 0.547%, the highest being 0.7% and the lowest 0.334%, the same plants yielding approximately the same amount of alkaloid from season to season. The leaves can be picked to best advantage from the time of flowering until the early berries begin to ripen. Later the leaves are richer, but are too small and sparse for harvesting.—*Chem. & Drugg.*, i/1914, 52.

Cultivation. Belladonna needs good drainage, warm hilly situation, and protection from direct sunlight.—E. M. Holmes, *Pharm. J.*, i/1926, 296. Cultivation in America.—Two crops of leaves are obtained—one at the end of July and the second in October. If the roots are not required for use they should be taken up in October and buried in a shed to preserve from frost, to be divided into five or six rootlets in the spring for propagation. This procedure is better than growing from seed. An acre yields six to eight thousand lb. of herb.

The highest alkaloidal content was obtained from a plot which had not been manured at all, but which was fully exposed to the sun. This content (1.035% in the dry leaf), from leaf collected September, 1911, was the highest ever recorded as having been obtained. The content from leaves under similar conditions, September, 1910, was 0.44%, June, 1911, 0.65%,—each the highest as against plants grown with artificial manures and far in excess of the yields from plants grown *in the shade*. Artificial manures, e.g., sodium nitrate, 1 cwt., with kainit, 3 cwt., per acre, increase the yield of *green plant*. This yielded 13½ tons per acre September, 1911, as against the plot with no manure, but sun, 8½ tons per acre.—F. Ransom and H. J. Henderson, *Chem. & Drugg.*, ii/1912, 443.

Basic slag, 2 cwt. per acre, and superphosphate, 5 cwt., applied March to April, had good effect on alkaloid yield—better than farmyard manure. The highest percentage of alkaloids has been observed in sunny seasons. Cultivated plants yielded as much as 1.08% alkaloid.—F. H. Carr, *Chem. & Drugg.*, ii/1912, 442.

Belladonna Pulverata (*B.P.* '32). Standardised to contain 0.28% to 0.32% of alkaloids, calculated as hyoscyamine. Ash, not more than 15%; acid-insoluble ash, not more than 3%.

Belladonnæ Radix (*B.P.* '32). Assayed as for *Belladonnæ Folia*, contains not less than 0.4% of alkaloids as hyoscyamine; other organic matter, not more than 4%; acid-insoluble ash, not more than 4%. The *U.S.P. X* requires the root to contain not less than 0.45% of its alkaloids and specifies maximum limits for stem bases and woody crowns of 10%, foreign organic matter, 2%, and acid-insoluble ash, 4%.

The assay gives a very low result if the directions are followed exactly. Quite satisfactory results are obtained if the 1.5 ml. of solution of ammonia is mixed before use with 2 ml. of water.—*P. A. W. Self, Pharm. J.*, i/1933, 243.

Alkaloidal Content. Roots grown by the late Dr. Martindale gave the following:—2nd year's growth, 0.605%; 4th year's, 0.51%.

J. J. Blackie found in Scottish-grown root, 1st year 0.72%, 2nd 0.65%, 3rd 0.66%, and 4th year 0.60%.

Atropina (*B.P.* '32). $C_{17}H_{23}O_3N = 289.2$. M.p. 114° to 116°. Ash, not more than 0.1%. Tests for limit of *l*-hyoscyamine and absence of apoatropine are included. The *U.S.P. X* alkaloid is required to comply with the platinic chloride test for most other alkaloids and with tests for apoatropine and belladonnine.

Deterioration of Atropine Eye Ointments. All the atropine eye ointments examined became weaker in atropine after storage. Ointments containing atropine base, with or without mercuric oxide, deteriorated most rapidly when stored in glycono-gelatin capsules. Glycono-gelatin does not accelerate the deterioration of ointments made with atropine sulphate. The alkaloidal content of eye ointment of atropine with mercuric oxide, *B.P.* '32, falls to about four-fifths of its original value in about a month and then remains nearly constant for a considerable time. The alkaloidal strength of iodoform and atropine eye ointment, *B.P.C.* '34, was well maintained during the period of the observations.—*N. L. Allport, Quart. J. Pharm.*, 1935, No. 3.

Atropinæ Sulphas (*B.P.* '32). $(C_{17}H_{23}O_3N)_2, H_2SO_4, H_2O = 694.5$. After drying at 136°, m.p. 195° to 196°. Loses at 105°, not more than 3%. Ash, not more than 0.1%. The salt is official in the *U.S.P. X*.

The melting-point is affected by the last minute trace of water which is not worth considering in the moisture determination, and it is therefore determined on the sample dried at 136°. When dried at this temperature the salt is comparatively stable in air.—*T. A. Henry, Pharm. J.*, i/1933, 86.

Drying of atropine sulphate at 105° may be far from complete, and a moisture determination carried out at 136° would be a better test for purity.—*G. R. Page, Quart. J. Pharm.*, 1934, 364.

Homatropinæ Hydrobromidum (*B.P.* '32). $C_{16}H_{21}O_3N, HBr = 356.1$. M.p. with partial decomposition, about 214°; ash, not more than 0.1%. Homatropinæ Hydrobromidum, *U.S.P. X*, should also comply with a test for alkaloid precipitated with tannic acid, and a test for alkaloids giving the Vitali reaction. It is also required to give no precipitate with platinic chloride.

A biological method for the assay of mydriatic and myotic alkaloids is described in *Methods of Analysis (A.O.A.C., 1930, 485)*.

BISMUTHUM

Bismuthi Carbonas (*B.P.* '32). Residue of Bi_2O_3 on ignition, 89% to 91%. Limit tests for lead, copper, sulphate, alkalis and alkaline earths, nitrate and chloride are included and also a test for absence of silver. Bismuthi Subcarbonas, *U.S.P. X*, after drying to constant weight at 100° yields, on ignition at a dull red heat, not less than 90% of Bi_2O_3 . Bismutum subcarbonicum, *P.G. VI*, contains 80.7% to 82.5% of bismuth.

Calcium is frequently present as impurity.—*H. Stout, Pharm. J.*, i/1921, 73.

Manufacture of "light" bismuth carbonate a trade secret. During conversion of bismuth subnitrate to oxycarbonate adsorption of traces of alkali

sults and no amount of washing will remove it. With tap-water, double composition between this alkali and calcium salts occurs, with consequent position of calcium carbonate. A method must be used to destroy the alkali. R. W. E. Stickings and H. C. Coupland, *Chem. & Drugg.*, i/1928, 605. A very dense variety is still official.—*Pharm. J.*, ii/1932, 67.

Bismuthi Citras (*B.P.C.* '34). Residue of Bi_2O_3 on ignition and re-ignition with nitric acid, not less than 55% and not more than 59%.

Liquor Bismuthi et Ammonii Citratis (*B.P.C.* '34). The following assay process is recommended as being more satisfactory than that of the *P.C.*: Dilute 10 ml. to 100 ml. To 25 ml. of the dilution add 50 ml. of water and sufficient nitric acid to produce a ppt. and to re-dissolve it. Add 50 ml. of water and strong solution of ammonia until a permanent ppt. is obtained, then add 2 ml. of nitric acid and heat to boiling. Add to the boiling solution a 10% solution of ammonium phosphate, at the rate of about 30 drops per minute, until all the bismuth is precipitated, then more quickly until 40 ml. in all has been added. Dilute to about 400 ml. with boiling water, heat on a water-bath for fifteen minutes, filter through a Gooch crucible, wash by decantation three times and then on the filter with a 3% solution of ammonium nitrate containing a few drops of nitric acid, dry, ignite and weigh. 1 g. of BiPO_4 is equivalent to 0.7654 g. of Bi_2O_3 .—C. T. Bennett and N. R. Campbell, *Quart. J. Pharm.*, 1932, 515.

Bismuthi et Sodii Tartras (*B.P.C.* '34). By precipitation as sulphide, re-precipitation as carbonate, and ignition to oxide, it contains from 38% to 44% of Bi.

Bismuthi Hydroxidum.—Corfield and Woodward were unable to substantiate the formula $\text{BiO}\cdot\text{OH}$ for a body made by the *FR. Cx.* or other method. The only pure compound they could obtain was one of the formula $\text{Bi}(\text{OH})_3$.—*Pharm. J.*, i/1924, 83.

Bismuthi Oxyiodogallas (*B.P.C.* '34). Assayed for I content by solution in sodium hydroxide, boiling with N/10 silver nitrate and nitric acid and back titration with N/10 ammonium thiocyanate, it contains not less than 20%. Residue of Bi_2O_3 , 43% to 45%. Bismutum oxyiodogallicum, *P. Helv. V*, should contain 20% to 24.5% of iodine and yield from 45% to 48.5% of Bi_2O_3 .

Bismuthi Salicylas (*B.P.* '32). Residue on ignition and re-ignition, not less than 62% and not more than 66% of Bi_2O_3 . A limit of salicylic acid of 0.1% is included. Bismuthi Subsaliylas, *U.S.P. X*, after drying to constant weight at 100° , yields 62% to 66% of Bi_2O_3 . Bismutum subsaliylicum, *P.G. VI*, contains 56.5% to 58.5% of bismuth.

Bismuthi Subchloridum (*B.P.C.* '34). Contains from 79% to 81% of Bi, determined by precipitation of sulphide, dissolving in nitric acid, re-precipitation as carbonate and ignition to Bi_2O_3 ; and not less than 12.5% of Cl by titration with silver nitrate and ammonium thiocyanate.

Bismuthi Subgallas (*B.P.C.* '34). Loses not more than 5% at 100° , and then yields by re-ignition with nitric acid from 52% to 57% of Bi_2O_3 . Limit of free gallic acid, by solubility in alcohol, not more than 0.1%. The *U.S.P. X* salt has the same standard on the dried substance. Bismutum subgallicum, *P. Helv. V*, yields 52% to 56.5% of Bi_2O_3 .

Bismuthi Subnitrates (*B.P.C.* '34). Residue of Bi_2O_3 , not less than 79% and not more than 81%. Should not effervesce with warm nitric acid. Bismuthi Subnitrates, *U.S.P. X*, yields not less than 79% of bismuth oxide after drying for twenty-four hours over sulphuric acid. Bismutum subnitricum, *P.G. VI*, contains 70.9% to 73.6% of bismuth. Bismutum subnitricum, *P. Helv. V*, contains 79% to 82% of bismuth calculated as Bi_2O_3 and is stated to correspond approximately to the formula $\text{Bi}(\text{OH})_2\text{NO}_3 + \text{O}Bi\text{NO}_3 + \text{O}Bi\text{OH}$ or $2\text{Bi}(\text{OH})_2\text{NO}_3 + \text{O}Bi\text{OH}$.

The proportion of N_2O_5 in this and other nitrates may be determined by the following method of the Board of Agriculture and Fisheries (Leaflet No. 18, p. 116):—

To 0.5 g. in a 500 ml. Erlenmeyer flask add 50 ml. of water and 20 ml. of sulphuric acid (sp. gr., 1.35) followed by 10 g. of reduced iron. Close the flask with a rubber cork through which passes a thistle funnel the head of which is half filled with glass beads, boil for five minutes and wash back into the flask any liquid among the beads. Boil for three minutes, then distil with 50 ml. of 50% sodium hydroxide, collecting the ammonia evolved in 50 ml. of N/10

sulphuric acid, and back titrate the excess acid with N/5 alkali. Conduct a blank experiment under the same conditions.—C. E. Corfield and G. R. Short, *Yearb. Pharm.*, 1924, 573.

Dragendorff's Test for alkaloids. Bismuth subnitrate 8, nitric acid, sp. g. 1.18, 20; add this solution gradually to a concentrated solution of potassium iodide, 22.7. Cool, decant from potassium nitrate formed, and dilute to 100 with water. The solution precipitates most alkaloids.

A suggested modification:—Dissolve bismuth carbonate 64 in hydrochloric acid 85 and add water 500 containing potassium iodide 166. Finally make up with water to 800. This eliminates nitric acid which causes decomposition and the proportion of potassium iodide is less. With this formula there is no trouble with crystals of potassium nitrate.

Thresh's Reagent. Bismuth citrate 2.4 g., water 20 ml., ammonia q.s. made up to 30 ml. with water and add to a solution of potassium iodide 2 g. in nitric acid 45 ml. Is similar in use to above.

Bismuthi Tribromphenas (B.P.C. '34). Assayed by precipitation, as for the subchloride, after decomposition with sodium hydroxide and dissolving the precipitate in hydrochloric acid, it contains not less than 40.5% and not more than 49.5% of Bi. A limit of free tribromophenol, by addition of excess sodium hydroxide to the alcohol-soluble matter and titration with standard hydrochloric acid, is equivalent to about 3%. Bismutum tribromophenylicum, *P.G.V.* should contain not less than 44.9% of bismuth. Bismutum tribromophenylicum *P. Helv. V*, yields from 50% to 55% of Bi_2O_3 .

Bismuthum Præcipitatum (B.P. '32). Determined by precipitation as phosphate, and ignition, it contains not less than 98.5% of metallic bismuth.

Detection of Silver in Bismuth Salts.

Dissolve 0.02 g. of bismuth carbonate in 2 ml. of dilute hydrochloric acid and add 2 ml. of 0.03% solution of *p*-dimethylaminobenzylidene-rhodanin and 1.8 ml. of distilled water. Add a few drops of water if necessary to make the liquid turbid. In the presence of 1 in 40,000 of silver the precipitate is red to violet. For bismuth salicylate, heat to boiling 0.5 g. with 5 ml. of dilute hydrochloric acid, shaking the tube. To 2 ml. of filtered liquid add 2 ml. of the above reagent and 3.8 ml. of water, or more if necessary, to produce turbidity. In the presence of 0.002% of Ag the ppt. is coloured violet.—J. F. Reith, *Pharm. J.*, i/1933, 316.

Sensitive Colour Reactions for Bismuth.

To a suitable volume of the aqueous solution to be tested, e.g. 10 ml., add 2 ml. of dilute hydrochloric acid and 0.5 g. of potassium iodide. Mix, and add 5 ml. of acetone or industrial spirit and 5 ml. to 10 ml. of ethyl acetate. Shake and allow to separate; a red colouration in the upper layer indicates bismuth. By suitable modification the test can be applied quantitatively and is suitable for the rapid determination of bismuth in urine and animal tissues.—A. D. Powell, *Quart. J. Pharm.*, 1933, 465.

Traces of bismuth in the presence of other metals can be separated by extraction, after preliminary treatment, with a solution of diphenylthiocarbazon in chloroform. After further treatment the bismuth compound is extracted with a mixture of 3 parts of amyl alcohol and one part of ethyl acetate. The colour of the solution is compared with those obtained from known amounts of bismuth.—L. A. Haddock, *Analyst*, 1934, 163.

BUCHU

Buchu (B.P. '32). The dried leaves of *Barosma betulina* (Thunb.) Bartl. and Wendl. only. Contains not more than 5% of its stems. Other foreign organic matter, not more than 2%. Ash not more than 5%. The *U.S.P. X* allows the dried leaf of *Barosma betulina* (Thunberg) Bartling et Wendl. or of *Barosma crenulata* (Linné) Hooker (short buchu) or of *Barosma serratifolia* (Curtis) Willdenon (long buchu). It should contain not more than 8% of its stems and not more than 2% of other foreign organic matter.

An account of the histology of buchu and of the leaves of other species of *Barosma*. A key is given for the identification of the powdered leaves of various species of *Barosma*.—T. E. Wallis and T. Dewar, *Quart. J. Pharm.*, 1933, 347.

CAFFEINA

Caffeina (*B.P.* '32). $C_8H_{10}O_2N_4 \cdot H_2O = 212:1$. M.p. after drying at 100° , 235° to 237° . Loss at 105° , not more than 8.5%. Ash, not more than 0.1%. Caffeina, *U.S.P. X*, should not lose more than 9% of its weight at 80° . Ash limit, 0.05%.

Caffeine and theobromine give no precipitate with Mayer's reagent, distinguishing them from the majority of alkaloids. Tea contains a minimum of 0.5% of caffeine and a maximum of 4.0%. Raw coffee, about 1.2%, and when roasted, about 1.3%. For manufacture, tea dust with the largest yield of alkaloid is extracted.

Tea.—When there is neither caffeine nor tannin present in quantity exceeding that which the compound of them (caffeine tannate) contains, the tea is pronounced by the taster as of good quality. Caffeine and tannin occur mostly (in good teas) in the ratio of 1:3—which is virtually the ratio in caffeine tannate. Cold water extracts only a very small proportion of the total caffeine in tea, though solubility is 1.35% at 16° . Caffeine is taken up in the same ways as tannate.

Coffee. The caffeine in tea, being in the form of caffeine tannate, is precipitated by the gastric juice and, therefore, the caffeine is probably not absorbed until it reaches the alkaline alimentary tract. In the case of coffee, however, in whatever form the caffeine may be present it is soluble in both alkaline and acid fluids and, therefore, the absorption in this case is probably in the stomach, hence the more prompt action as restorative.

Decaffeinated Coffee. The amount of caffeine removal in current specimens approximates well over 90%, assuming that 1.2% of caffeine by weight was originally present.—*J. Amer. med. Ass.*, ii/1928, 883.

Caffeinae Citras (*B.P.C.* '34). $C_8H_{10}O_2N_4 \cdot C_6H_8O_7 = 386.2$. By extraction with chloroform from a solution made alkaline with sodium hydroxide and drying at 100° , the anhydrous caffeine obtained is from 46% to 51%. Loss at 80° , not more than 5%. Ash, not more than 0.1%. Caffeina Citrata, *U.S.P. X*, loses not more than 5% at 80° and then contains from 48% to 50% of anhydrous caffeine. Ash limit, 0.1%. Caffeinum citricum, *P. Helv. V*, contains not more than 2% of moisture and from 48.8% to 50.8% of anhydrous caffeine. **Assay:** Dissolve 0.5 g. in 2.5 ml. of water; add, after cooling, 25 g. of chloroform and 2 g. of 30% solution of sodium hydroxide, and shake for 5 minutes; add 0.5 g. of powdered tragacanth and shake again. After 5 minutes, filter and distil off the chloroform from 20 g. of the filtrate in a tared flask; dry the residue for 30 minutes at 103° to 105° and weigh, adding 0.0017 g. of caffeine to the weight obtained. The result gives the weight of anhydrous caffeine in 0.4 g. of the caffeine citrate.

Caffeina et Sodii Benzoas (*B.P.* '32). The dried substance contains 47% to 50% of $C_8H_{10}O_2N_4$ and 50% to 53% of $C_7H_5O_2Na$. Loss at 105° , not more than 5%. Caffeine is determined as in Caffeinae Citras; benzoic acid is extracted with ether from the aqueous liquids and washings from the caffeine extraction made acid with dilute sulphuric acid; after evaporation of the ether, the residue is titrated in alcoholic solution with N/10 sodium hydroxide to phenol red and calculated to the sodium compound. M.p. of the separated caffeine, 235° to 237° , and of the separated benzoic acid, 121° to 122° . Caffeinae Sodio-Benzoas, *U.S.P. X*, loses not more than 5% at 80° and then contains 47% to 50% of anhydrous caffeine and 50% to 53% of sodium benzoate. In the assay, chloroform is used to extract the benzoic acid, which is afterwards titrated with N/10 barium hydroxide to phenolphthalein. Coffeinum-Natrium benzoicum, *P.G. VI*, contains not less than 38% of anhydrous caffeine.

Caffeina et Sodii Salicylas (*B.P.C.* '34). Assayed as Caffeina et Sodii Benzoas, it contains 47% to 50% of anhydrous caffeine, and 50% to 53% of sodium salicylate, calculated with reference to the substance dried at 105° . Loss at 100° , not more than 5%. Caffeinae Sodio-Salicylas, *N.F. V*, contains from 46% to 50% of anhydrous caffeine after drying at 80° . Coffeinum-Natrium Salicylicum, *P.G. VI*, should yield not less than 40% of anhydrous caffeine. It is assayed as follows:—

Dissolve 0.5 g. of caffeine sodium salicylate in 1 ml. of water in a 50 ml. measure. Add to the solution 25 g. of chloroform and 2.5 g. of sodium hydroxide solution. Shake thoroughly for 5 minutes. After adding 0.3 g. of tragacanth, shake again

for several minutes, and after a further 5 minutes pour 20 g. of the chloroform solution (equivalent to 0.4 g. of the sample) through a little wool into a weighed flask. On evaporating the chloroform and drying the residue at 100°, the residue must be at least 0.16 g., representing 40% of caffeine.

An official quantitative method for the determination of acetylsalicylic acid, phenacetin and caffeine in tablets is described in Methods of Analysis (*A.O.A.C.* 1930, 448).

Caffeinæ Hydrobromidum (*B.P.C.* '34). $C_8H_{10}O_2N_4 \cdot HBr \cdot 2H_2O = 311.1$. Yields from 60% to 63% of anhydrous caffeine. Ash, not more than 0.1%.

Theobromina (*B.P.C.* '34). $C_7H_8O_2N_4 = 180.1$. Loss at 100°, not more than 3%. Ash, not more than 0.1%. A caffeine limit, by extraction with chloroform from sodium hydroxide solution, is equivalent to 1%.

Cocoa. The ground nibs of *Theobroma Cacao* from which most of the fat has been removed.

Cocoa is sometimes treated with an alkali or an alkaline salt, such as potassium carbonate, to render it "soluble," the alkali probably producing a more perfect emulsion of the fat.

Before and after treatment with alkali, cocoa shows essentially the same lack of solubility, and hence the designation "soluble cocoa" is misleading and deceptive. (U.S. Board of Food Inspection.)

In pure untreated cocoa, the ash should generally be below 5.5%, with an alkalinity not exceeding 3.75, while with cocoas treated with alkali the ash is often as high as 8.5%, with an alkalinity exceeding 6. (Azor Thurston *Pharmaceutical and Food Analysis*, 1923.) Allen also states that an alkalinity of more than 7.5 is indicative of treatment, the alkalinity being the number of ml. of N/10 acid necessary to neutralise the ash from 1 g. of sample.

A number of samples were examined (1925) by the late Dr. Martindale, and it was found that in several cases the high ash and alkalinity were suggestive of the use of alkali in their preparation. The % ash varied from 2.8 to 7.5, the average being 5.7. The alkalinity varied from 3.5 to 11.0, the average volume of N/10 acid required to neutralise 1g. being 7.5 ml. None of the samples contained added starch. When treated with water as directed, the sample with high alkalinity did not give a better suspension than the untreated samples.

The examination of a number of cocoas on the market showed moisture to range from 3% to 8%. *Nitrogenous matter* ($N \times 6.3$) 19% to 20%, *fat* 26% to 31%, *mineral matter* 3.9% to 8.8%, *theobromine* 1.7% to 2.0%.—*Lancet* i/1905, 316.

Cocoa red is an astringent matter found in cocoa, which on saponification breaks up into glucose, tannin, resin and a phlobaphene.

Chocolate and Cocoa, a Disparagement of. When containing a considerable proportion of theobromine, chocolate and cocoa, if taken in excess, have been thought harmful. Theobromine is said to be a poison, coarsening and degrading the brain by inhibiting growth. It was stated that cocoa retards the absorption of the proteins and fats of the food, especially those forms of cocoa from which the fat has been partially removed, while on the other hand cocoa with a large percentage of oil delays gastric secretion and may give rise to dyspepsia. The detrimental effects were, it was claimed, in the main, due to the theobromine.

Neither by itself nor in combination with milk can cocoa be regarded as an important source of food protein.—*Brit. chem. Abstr.* (A), 1927, 170.

"*Couvertures*" is the trade name for a good refined block chocolate, made by wholesale chocolate manufacturers for selling to makers of toffees, marzipan centres, etc., who do not make their own chocolate, but require it for dipping their sweets. The couverture is simply melted down and the sweets dipped.

Theobromina et Sodii Salicylas (*B.P.* '32). Loss at 110°, not more than 5% and then contains not less than 46% of $C_7H_8O_2N_4$, not less than 41% of $C_7H_5O_3Na$, and not more than 6.9% of Na additional to that contained in the sodium salicylate. Assayed by the processes of the *B.P.* '32; for theobromine about 1 g. in 10 ml. of water is shaken with 2 ml. of N/1 sodium hydroxide and 0.6 ml. of dimethyl sulphate for five minutes and set aside, with frequent shaking for thirty minutes; a further 3 millilitres of N/1 sodium hydroxide is added and shaken well for one or two minutes, and the caffeine extracted immediately with successive portions of chloroform; the washed mixed chloroform solution are evaporated and dried at 100° for 1 hour; 1 g. of the anhydrous caffeine obtained is equivalent to 0.9278 g. of $C_7H_8O_2N_4$. Salicylic acid is determined on a solution from which the theobromine has been precipitated with ammonia, the mixture being allowed to stand for 3 hours, then filtered and the

rate acidified, by extraction with ether, finally titrating in alcoholic solution with N/10 sodium hydroxide to phenol red. Additional sodium is titrated in an aqueous solution with N/1 hydrochloric acid to phenol red. A limit test for caffeine equivalent to 0.5% is included. Theobromina Sodio-Salicylas, *S.P. X*, should yield not less than 46.5% of theobromine and not less than 46% of salicylic acid, after drying at 110°, at which temperature the loss should not more than 10%. 2 g. of the dried substance requires not more than 10 ml. of N/1 hydrochloric acid to neutralise to phenolphthalein; theobromine is filtered from this neutralised solution, made just alkaline to litmus with ammonia, and dried at 100°, a correction being added for the solubility in liquid and washings; salicylic acid is extracted from these with chloroform. Theobromino-natrium salicylicum, *P.G. VI*, contains not less than 40% of theobromine. Theobromino-natrium salicylicum, *P. Helv. V*, contains not more than 5% of moisture, 10.5% to 10.7% of NaOH, and from 45% to 48% of theobromine.

Theophyllina (*B.P.C. '34*). $C_7H_8O_2N_4 \cdot H_2O = 198.1$. M.p., 265° to 270°. Loses at 100°, not more than 9.5%. Ash, not more than 0.1%. The *U.S.P. X* shows the same moisture limit for Theophyllina.

Theophyllina et Sodii Acetas (*B.P. '32*). By treatment with dimethyl sulphate and sodium hydroxide, followed by extraction with chloroform, it yields caffeine equivalent to not less than 55% of anhydrous theophylline. Theophyllino-natrium aceticum, *P. Helv. V*, contains from 3% to 4% of moisture, equivalent to 1 molecule of water of crystallisation, and about 65% of theophylline, but no assay process for the latter is prescribed. In the assay processes for Theophyllina et Sodii Acetas and Theobromina et Sodii Salicylas, the dimethyl sulphate must be in slight excess at the end of the reaction, and the caffeine must be shaken out rapidly after the addition of the sodium hydroxide, since it is quickly decomposed by strong alkalis.—*P. W. Self, Pharm. J.*, ii/1933, 244.

Maté. Analysis showed caffeine 2.02%, sugar as glucose 6.08%, tannin 12.22%; 3 and 10 minutes infusion (the 10 minutes being on the old marc) at about 90° gave total dissolved substances respectively 21.8%, 31.8%, organic matter 10.4%, 28.4%. Mineral matter (ash) 2.4%, 3%, tannin 7.68%, 11.08% and caffeine 1.39% and 1.70%. The second figures in each case indicate totals.

The best method of preparing the "tea" is by first moistening the leaf thoroughly with boiling water and then, after a few minutes, adding the remainder of the boiling water and allowing to infuse for 15 minutes.

A mild heart stimulant if taken periodically. Leaving it off after having taken it for some time may, it is said, cause prostration. Mortality from heart disease in the Argentine is greater than elsewhere—ascribed to maté.

More than 18,000,000 people in S. America drink maté. Thought to ward off rheumatism, and produces exhilarating yet soothing effect on nerves and has very sustaining properties. Principal beverage of rural working classes in the Argentine, Paraguay and Brazil.—*J. trop. Med. (Hyg.)*, 1925, 320.

CALCIUM

Calcii Carbonas (*B.P. '32*). $CaCO_3 = 100.1$. Loses at 100°, not more than 1% and then contains not less than 98.5% of $CaCO_3$. Calcii Carbonas Præcipitatus, *U.S.P. X*, after drying at 200°, contains not less than 98% of $CaCO_3$ and is assayed by precipitation with excess N/10 oxalic acid in ammoniacal solution, and back titration of the acidified filtrate with N/10 potassium permanganate. Calcium Carbonicum Præcipitatum, *P. Helv. V*, contains from 98.75% to 100.5% of $CaCO_3$. The bulk density of Calcium Carbonicum Præcipitatum ad usum externum, *P. Helv. V*, is controlled by the following test:—Introduce without shaking 5 g. into a 100 ml. graduated cylinder and allow the cylinder to fall lightly on the palm of the hand ten times; the powder should measure not less than 65 ml.

Creta (*B.P.* '32). Dried at 100° it contains not less than 97% of the pure substance and at that temperature loses not more than 1%. It is assayed with excess of N/1 hydrochloric acid and titration with N/1 sodium hydroxide using methyl orange as indicator. *Creta Præparata, U.S.P. X*, contains 97% after drying at 200°.

Calcium Carbide. CaC_2 . Grey masses, becoming white when moist. Evolves acetylene when brought into contact with water. May be used as a test for, and in the preparation of, absolute alcohol. Requires special storage.

Calcium Cyanamide, *syn.* ★Nitrolim (T.M. 437595) is formed when nitrogen is passed over calcium carbide heated to 1000° : $\text{CaC}_2 + \text{N}_2 = \text{CaCN}_2 + \text{C}$. The nitrogen of same interacts with water under pressure, thus:—

$$\text{CaCN}_2 + 3\text{H}_2\text{O} = \text{CaCO}_3 + 2\text{NH}_3.$$

The nitrogen must first be freed from oxygen. This is effected by fractional distillation of liquid air. The above method of fixing atmospheric nitrogen is the Frank-Caro process. Calcium cyanamide is a black powder, containing 15% to 20% nitrogen and about 20% free lime. As a fertiliser it is valuable on acid or "sour" soils and is usually treated with oil to render it granular and to reduce its dusty and corrosive nature.

Calcii Hydroxidum (*B.P.* '32). $\text{Ca(OH)}_2 = 74.1$. Assayed by digestion with sucrose solution, filtration, and titration of an aliquot part with N/10 hydrochloric acid to phenolphthalein, when it should contain not less than 90% of Ca(OH)_2 . Samples usually contain about 0.7% to 0.8% of aluminium, iron and matter insoluble in hydrochloric acid, which is above the *B.P.* limit of 0.5%.

Calcii Oxidum (*B.P.C.* '34). $\text{CaO} = 56.08$. Loss on ignition not more than 10%. The ignited substance should contain not less than 95% of CaO when determined by the *B.P.* method for *Calcii Hydroxidum*. *Calx, U.S.P. X*, loses not more than 10% on ignition to constant weight with a Bunsen lamp, and then contains not less than 95% of CaO . It is assayed by the oxalic acid precipitation method used for *Calcii Carbonas Præcipitatus, U.S.P. X*.

Calx Chlorinata (*B.P.* '32). Contains not less than 30% *w/w* of available chlorine. Determined by titration, with N/10 sodium thiosulphate, of the iodine liberated when a suspension with potassium iodide is treated with acetic acid. The *U.S.P. X* fixes the same standard of available chlorine, determined in the same manner.

Decomposition of Bleaching Powder. According to modern views, when moist CO_2 acts on bleaching powder chlorine only is given off (no hypochlorous acid as originally thought). Air free from CO_2 very slowly liberates hypochlorous acid, but no chlorine. With air containing CO_2 , a mixture of hypochlorous acid and chlorine is obtained, the proportion of the former decreasing with time. These points are explained on assumption that the action of chlorine on alkali is reversible:



The action of air in promoting bleaching is therefore due to removal of lime from the powder by CO_2 . The bleaching action is further accelerated by the addition of common salt or calcium chloride.

Stabilised Bleach, i.e., bleaching powder mixed with 20% powdered quicklime, retains its available chlorine in hot climates, e.g. a sample leaving England at 25% and arriving in Madras showing 18.4%, fell to 10% in 42 weeks while ordinary bleaching powder (leaving England at 35%) fell to 0.42% in 14 weeks. After 2 years, however, it was found to contain 5.9% calcium chlorate—this would not do for sterilising water, owing to its taste.—A. F. Macculloch *J. Soc. chem. Ind., Lond., 1921, 40, 240T; Yearb. Pharm., 1922, 119.*

Water Sterilisation with chlorine and chlorinated lime, see Vol. I, p. 41, and Notes on Water Analysis, this Volume.

Eusol.—Keep in stoppered bottles away from the action of light. The preparation maintains its strength for 3 weeks in cold weather. In hot weather it should not be kept more than 1 week. It is preferably made fresh each day for use on the day following. Dakin's solution, however, keeps much better.

Assay. Place 25 ml. of the solution in a flask, add about 1 g. of potassium iodide and 5 ml. of acetic acid and titrate with N/10 sodium thiosulphate solution, using starch paste as indicator. Each ml. of the thiosulphate solution employed shows 0.003546 g. of available chlorine.

Solutions of this nature may be slightly pink in colour if manganese is present in the bleaching powder.

Bactericidal Power. Hypochlorous acid is a more potent bactericide than its salts. The acid is stated to be the most powerful antiseptic known. It was found to be as active against anthrax spores as against non-spore-bearing organisms (2 minutes' contact).

Dakin's Solution

Strength. Dakin's (weaker) solution, and his stronger solution on dilution, are approximately 1/5 the strength of *Liquor Sodæ Chlorinatæ*, and there is a considerable excess of sodium carbonate employed. This is neutralised with citric acid as described in Vol. I, p. 44.

Some confusion arises in the expression of the strength of preparations of this kind. This weaker preparation contains 0.5% to 0.55% available chlorine. The stronger Dakin's solution is approximately 7 times this strength.

Bactericidal Power. The antiseptic power of sodium hypochlorite using *Staphylococcus Aureus* with 2 hours' contact in water, it is stated, lies between 1 : 500,000 and 1 : 1,000,000, while in the presence of blood serum the necessary concentration is between 1 : 1500 and 1 : 2000.

By "hypochlorite" is clearly meant the 0.5% NaOCl contained—in other words, to kill the organism in water in 2 hours between a 1 in 2500 and a 1 in 5000 dilution of the solution is requisite, whilst in the presence of serum a dilution between 1 in 7.5 and a 1 in 10 is necessary. The solution is hence not extraordinarily powerful.

CAMPHORA

Camphora (*B.P.* '32). $C_{10}H_{16}O = 152.1$. Both the synthetic and natural substances are official. M.p., 174° to 177° . Residue on volatilisation not more than 0.05%. The natural product, as *Camphora*, only is official in the *U.S.P.* X, the specific rotation being used as an identity test; residue on sublimation, not more than 0.05%. *Camphora* and *Camphora synthetica* are official in the *P.G.* VI, the former melts at 175° to 179° and has a specific rotation for a 20% solution in absolute alcohol of $+44.22^{\circ}$, whilst the latter melts at not lower than 170° and has a specific rotation of -2° to $+5^{\circ}$.

An official quantitative method for the determination of camphor (optically active) is described in *Methods of Analysis* (*A.O.A.C.*, 1930, 458).

Camphor may be determined by means of the reaction with 2 : 4-dinitrophenylhydrazine, the resulting hydrazone being collected, dried and weighed. It will be possible to formulate pharmacopœial requirements based on this method.—C. H. Hampshire and G. R. Page, *Quart. J. Pharm.*, 1934, 558.

Manufacture of Synthetic Camphor. Pinene ($C_{10}H_{16}$) is obtained by fractional distillation of oil of turpentine previously freed from resin. The pinene saturated with dry hydrochloric acid is the old-fashioned artificial camphor. The subsequent processes consist of splitting off the hydrochloric acid to obtain camphene, which is isomorphous with pinene. This substance, dissolved in glacial acetic acid, with a little sulphuric acid, yields bornyl acetate, and this saponified becomes borneol, which is identical with Borneo camphor. After oxidation synthetic camphor results, and this corresponds exactly with the Japanese and Chinese camphor, except in optical properties. The synthetic is optically inactive.

The manufacture of celluloid takes 80% of the world's production of camphor. The film industry takes a lot. The manufacture of synthetic camphor is difficult economically, being dependent on a plentiful supply of turpentine rich in pinene, and on its market value. One type competes against the other. Darmois has produced the synthetic variety of optical activity equivalent to the natural.—*Chem. & Drugg.*, ii/1926, 405. See also *Pharm. J.*, i/1924, 234.

Linimentum Camphoræ. The optical rotation of the camphor cannot now be used to check the result of the evaporation test, since both the natural and the synthetic varieties are official.—*Chem. & Drugg.*, ii/1932, 421.

Oleum Camphoræ Rectificatum (*B.P.C.* '34). The f.p. of a mixture of 0.5 g. of the oil, 1.5 g. of eucalyptol and 2.1 g. of *o*-cresol is not below 40° ,

equivalent to not less than 35% of cineole. Sp. gr., 0.875 to 0.900. α_D , + to +24°. n_{D40° , 1.465 to 1.470.

The two commercial varieties are **white camphor oil** and **brown camphor oil**. The former is the early fraction of the natural oil, obtained as by-product in the manufacture of camphor; the sp. gr. is lower than 0.99. Brown camphor oil is the higher boiling fraction, the sp. gr. varies from 1.00 to 1.040; oil of the higher figure contains a large proportion of safrole, while oil with a gravity in the neighbourhood of 1.000 is the by-product after removal of the safrole by refrigeration. Camphor oil containing a large proportion of safrole and with a specific gravity of about 1.065 is sold as **artificial sassafras oil**.

CANNABIS

Cannabis (*B.P.C.* '34). The drug may now be obtained from plants grown in India, Germany, America and South Africa and contains not more than 10% of fruits, large foliage leaves, and stem over 3 mm. in diameter, and not more than 2% of other foreign organic matter. Acid-insoluble ash limit, 5%. Matter soluble in alcohol after drying at 100°, not less than 10%. Cannabis, *U.S.P.* X, is of the same standard as the *B.P.C.* substance but is also standardised by the inco-ordination produced in dogs by a fluid extract prepared in the official manner.

In Northern India the resin exuded is mixed with tobacco and smoked or taken in the form of bhang as a drink. The native then passes into a state of languid ease, accompanied by an elated sense of superiority. There is also induced an altered relationship to time and space, so that minutes become hours and feet furlongs.—W. E. Dixon, *Chem. & Drugg.*, i/1928, 747.

Test for Recognition of Hashish : Beam's Test. The suspected material is extracted with petroleum ether of low boiling-point, and the extract filtered and evaporated to dryness. Both extraction and evaporation should be carried out in the cold. In the presence of a considerable quantity of hashish a marked amount of tar-like residue is obtained, but it is sufficient for the reaction if only a faint yellow stain is left. To the residue a weak alcoholic solution of potassium or soda (about N/10) is added and the liquid allowed to evaporate at room temperature. In presence of hashish a rich purple or reddish-purple colour develops, which, on dilution with water, takes on a more bluish cast. Hashish is frequently sold dissolved in fat or oil, and for such alcohol is best. Extracts of Indian hemp and Ceylon samples did not respond. Samples of ganja, charas and majun from India and a plant grown in Egypt responded perfectly. The ordinary hashish sold in Egypt is largely of Greek origin, and of a large number of samples tested since 1909 not one has failed to respond. Soil, climate, cultivation, and curing influence the chemical composition. The following is suggested as a useful presumptive test to which hashish or other *Cannabis* preparations from India, Egypt, Greece, Sudan, and Uganda all respond. The petroleum ether extract is made as usual, and the evaporation of the solvent is carried out in a short test-tube. To the residue is added a few millilitres of reagent prepared by saturating absolute alcohol with dry hydrogen chloride gas. In the presence of *Cannabis* extract the liquid acquires a bright cherry-red colour which disappears on dilution with alcohol or water. Trials were made with a number of plant extracts and over 200 alkaloids, glycosides, etc., but in no case was a similar reaction obtained. Certain volatile oils—e.g., *origanum* and *santal*—give a similar reaction, but the colour is far less intense for similar amounts of material.—W. Beam, Wellcome Res. Lab., Khartoum, per *Chem. Drugg.*, 1916, 12.

Determination of Physiological Activity of Hemp Resin. The activity of charas, ganja and bhang is associated with their resins, but the resin content is not a measure of potency. There is a definite relationship between the specific rotation of the drug and its physiological activity, and a polarimetric method has been devised for its assay. The specific rotation of the resin of good and fresh charas is about -105° whilst that of older and inferior material is as low as -64° ; that of ganja of good quality is about -90° , and of inferior quality about -60° or less.—M. N. Ghose and S. W. Bhattacharjee, *Analyst*, 1935, 31.

Extractum Cannabis.—This material is sometimes submitted to a biological test by administering doses of a soft extract, equal to 0.25 g., to one or two cats. The extract is given in gelatin capsules which are placed at the back of the mouth and so readily swallowed. Active extracts produce some intoxication and inco-ordination of movement; most striking is the inclination to stay for several seconds in an awkward posture. The effect may last for 3 or 4 hours.

CANTHARIDINUM

Cantharidinum (*B.P.* '32). $C_{10}H_{12}O_4 = 196.1$. M.p., 216° to 18° . Ash, not more than 0.1%. Cantharidin in preparations containing it may be detected by the following process:—To 20 ml. of the liquid add sufficient H_2SO_4 to make it *slightly* acid and extract 3 or 4 times with chloroform. Evaporate the $CHCl_3$ to about 3 ml., add 0.2 ml. of a vegetable oil such as sesame or cotton-seed, evaporate and dry at 100° to remove the $CHCl_3$. Apply to the skin on a very small pad of lint (the lint should be *saturated* with the oil) and leave in contact for about 12 hours. If cantharidin is present, a blister will form or the skin be much reddened. Taking 20 ml. of a liquid, the test will show 5 to 10 parts of cantharidin per million. If a larger volume is taken the test may, of course, be made still more delicate.

Cantharis (*B.P.C.* '34). Foreign organic matter, not more than 2%. Moisture, not more than 10%. Cantharis, in powder, is adjusted, by the addition of powder of higher or lower catharidin content, to contain not less than 0.6% of cantharidin. It is assayed by maceration with chloroform acidified with hydrochloric acid, filtration and evaporation of an aliquot part; after removal of the fat with light petroleum the insoluble residue is treated with N/1 sodium hydroxide and warmed with 5% potassium permanganate solution; the mixture is made strongly acid with 40% sulphuric acid, chloroform and ferrous sulphate are added, and the cantharidin extracted with chloroform; the residue, after evaporation of the chloroform, is finally weighed after drying at 65° . Cantharis, *U.S.P. X*, yields not more than 10% of moisture and not less than 0.6% of cantharidin, by extraction with a mixture of benzene, petroleum-ether and hydrochloric acid at 40° ; after evaporation of the solvent from an aliquot part, followed by evaporation with chloroform, the residue is washed with a mixture of absolute alcohol and petroleum-ether saturated with cantharidin, and dried at 60° for 30 minutes. Cantharides, *P.G. VI*, should yield not less than 0.7% of cantharidin by the process given. Cantharis, *P. Helv. V*, contains not less than 0.7% of cantharidin, and the powder when prescribed except for plasters is adjusted with lactose to contain 0.6%.

CAPSICUM

Capsicum (*B.P.* '32). Contains not more than 3% of calices and pedicels, not more than 1% of stalks and foreign organic matter, and yields not more than 7% of ash. Capsicum, *U.S.P. X*, contains not more than 3% of stems and calyxes and not more than 1% of other foreign organic matter; non-volatile ether-soluble extractive, not less than 12%; acid-insoluble ash, not more than 1.25%. In *U.S.P. X* the botanical source of capsicum is given as *Capsicum frutescens* Linné, grown in Africa.

The Food and Drug Administration of the U.S. Dept. of Agriculture define cayenne pepper, cayenne, as the dried, ripe fruit of *Capsicum frutescens* L., *C. baccatum* L., or some other small-fruited species of *Capsicum*. Contains not less than 15% of non-volatile ether extract, not more than 1.5% of starch, not

more than 28% of crude fibre, not more than 8% of total ash, nor more than 1·25% of ash insoluble in hydrochloric acid.—*S.R.A., F.D.*, No. 2, Rev. 4., Aug. 1933.

Extraction of Capsaicin and its Colorimetric Determination. 100 g. oleoresin (*U.S.P. X*, extracted with ether) is mixed thoroughly with twice volume of liquid paraffin and shaken out with three successive 200 ml. portions of alcohol (57%). The mixed alcoholic extracts are shaken with 100 ml. liquid paraffin, the alcoholic layer is separated and the alcohol distilled off. The cooled aqueous residue is extracted with ether, emulsification being prevented by the addition of sodium chloride. The ether is removed by distillation and the oily residue is boiled for 10 minutes, with occasional stirring, with 200 ml. of lithium hydroxide (carbonate-free) and 200 ml. of water. After standing overnight carbon dioxide is passed intermittently through the mixture for 24 hours, water being added if it becomes too thick, and it is again allowed to stand overnight. The precipitate is collected, washed and dried at a low temperature. The precipitate and filter are boiled under a reflux condenser with 500 ml. of light petroleum for 15 to 20 minutes, the hot light petroleum decanted on to filter and the clear filtrate set aside below 0° to crystallise. The crystals are rapidly filtered and transferred to a securely stoppered vial. The first precipitate and the filters should be re-extracted with light petroleum. At least 5 g. capsaicin is obtained from 100 g. of oleoresin of Mombassa capsicums. It has a m.p. of 64°, and its acidity is detectable in a dilution of 1 : 10,000,000.

Determination. The determination depends on the production of an intense blue colour with vanadium oxychloride. A 2% *w/v* extract of capsicum (dried overnight in a desiccator) prepared by maceration for 30 to 60 minutes in dry acetone, or a 0·2% solution of the oleoresin in dry acetone is prepared, and also a standard 0·02% solution of capsaicin coloured with an acetone extract of capsaicin-free paprika to match the test solution. Standard tubes are prepared with from 1·5 ml. upwards of capsaicin solution diluted with coloured acetone to 5 ml. To each tube is added one drop of a 1% *w/v* solution of vanadium oxychloride in carbon tetrachloride for each thousandth part per cent. capsaicin present. The reagent is then added drop by drop to the unknown until no deepening in colour is observed; excess must be avoided since the colour changes to green. The colour slowly fades after the reaction.—*L. Tice, Amer. J. Pharm.*, 1933, 320.

Oleoresin of Capsicum. The so-called oleoresins of capsicum vary in appearance, solubility and degree of pungency according to the solvent used for extraction.

Oleoresin of capsicum, *B.P.C.* '34, is prepared by extracting an ether oleoresin with alcohol (90%) and is soluble in ether, alcohol (90%), acetone, benzene, chloroform, petroleum spirit, fixed oils and turpentine. It has a greater pungency value than any of the other oleoresins of capsicum, the pungency being about three or four times that of oleoresin of capsicum, *B.P.C.* '23, which was extracted with alcohol (60%).—*H. Berry, Quart. J. Pharm.*, 1935, No. 3.

CARBO

Carbo (*B.P.C.* '34). Ash, not more than 7%. Moisture, not more than 15%. Carbo Ligni, *U.S.P. X*, yields not more than 7% of ash.

A test for activity of medicinal and other charcoals by exposure to water and other vapours. Active charcoal will absorb 50% to 100%, or even more, of moisture. The water figure is slightly higher than that for alcohol and turpentine. *Pulv. Carbo. Lig.* as ordinarily dispensed for medicinal purposes is inactive. The author suggests improvements in the manufacture, and adoption in the *B.P.* of tests for activity.—*H. Brindle, Pharm. J.*, ii/1928, 1.

Astonishing variety in the potency of different brands. A comparison of the adsorptive powers of thirty samples (using methylene blue as the substance to be adsorbed) showed coefficients varying from 85 to 0·5. Wholesale prices range from 15/- to £67 : 4 : 0 per cwt.—*N. Mutch, Brit. med. J.*, i/1934, 320.

Carbonei Dioxidum (*B.P.* '32). $\text{CO}_2 = 44\cdot00$. By measurement of the volume absorbed when passed into 50% *w/v* potassium hydroxide solution at N.T.P. it contains not less than 99% *v/v* of CO_2 .

CARDOMOMUM

Cardamomum (*B.P.* '32). Separated from the fruits when required for use, and contains not more than 3% of foreign organic matter. Ash, not more than 6%. *Cardamomi Semen*, *S.P. X*, should be recently removed from the capsules and yield not more than 5% of acid-insoluble ash.

The *B.P.* limit of impurity should apply to the fruit and not to the seed, which must not be separated from the fruit until required for use and is therefore protected from adulteration.—*Pharm. J.*, ii/1932, 68.

The Food and Drug Administration of the U.S. Dept. of Agriculture define cardamom as the dried, nearly ripe fruit of *Elettaria cardamomum* Maton. Cardamom seed is the dried seed of cardamom. Contains not more than 8% of total ash nor more than 3% of ash insoluble in hydrochloric acid.—*S.R.A., F.D.*, No. 2, *Rev.* 4, Aug. 1933.

Oleum Cardamomi (*B.P.C.* '34). Sp. gr., 0.923 to 0.945; $\alpha_D +20^\circ$ to $+44^\circ$; n_{D20° , 1.461 to 1.467. Ester value, 90 to 156. It should be soluble in 4 volumes of alcohol (70%, sp. gr. 0.8896 to 0.8901). *Oleum Cardamomi*, *F. V*, has a sp. gr. at 25° of 0.924 to 0.947. Rotation in a 100 mm. tube at 25° , $+22^\circ$ to $+44^\circ$.

The husks are for practical purposes inert. The green cardamoms yield more oil than the bleached. Imported decorticated seeds yield less oil than those recently removed from the husk. Loss of oil from the husk-protected seed on opening over eight months is small; decorticated seeds lost 80% of oil on opening over the same period. The oil requires not less than three hours for saponification.—Clevenger, *J. Ass. off. agric. Chem.*, 1934, 283.

CARUM

Carum (*B.P.* '32). Limits: for foreign organic matter, 2%; for ash, 9%; for acid-insoluble ash, 1.5%. *Carum*, *U.S.P. X*, contains not more than 3% of other fruits, seeds or foreign organic matter; acid-insoluble ash, not more than 1.5%. *Fructus Carvi*, *P.G. VI*, must yield not less than 4% of volatile oil.

The Food and Drug Administration of the U.S. Dept. of Agriculture define caraway, caraway seed, as the dried fruit of *Carum carvi* L. Contains not more than 8% of total ash or more than 1.5% of ash insoluble in hydrochloric acid.—*S.R.A., F.D.*, No. 2, *Rev.* 4, Aug. 1933.

Oleum Cari (*B.P.* '32). Assayed by the same method as for *Oleum Anethi*, *B.P.* '32, it contains from 53% to 63% *w/w* of carvone. Sp. gr., 0.910 to 0.920. $\alpha_D +70^\circ$ to $+80^\circ$. n_{D20° , 1.485 to 1.492. Soluble in one volume of alcohol (90%, sp. gr., 0.8334 to 0.8340) and in 7 volumes of alcohol (80%, sp. gr., 0.8634 to 0.8640). *Oleum Cari*, *U.S.P. X*, should contain not less than 50% *v/v* of carvone; estimated by measurement of the oil remaining after treatment with sodium sulphite.

Determination of carvone in caraway oil.—Bennett and Cocking (*Quart. J. Pharm.*, 1931, 580) give a method of applying the hydroxylamine reaction.

Caraway oil consists mainly of carvone, sp. gr. 0.964, and limonene, sp. gr. 0.846; the sp. gr. of the oil is therefore a good indication of the proportion of carvone.

CARYOPHYLLUM

Caryophyllum (*B.P.* '32). Clove should contain not more than 1% of its stalks and not more than 1% of foreign organic matter. Limits: ash, 10%; acid-insoluble ash, 0.75%. Tests for limit of stalks and absence of clove fruits and cereals are included.

Caryophyllus, *U.S.P. X*, should yield not less than 15% of volatile ether-soluble extractive and not more than 10% of crude fibre; the limits for stem, foreign organic matter and acid-insoluble ash are the same as in the *B.P. '32*.

Flores *Caryophylli*, *P.G. VI*, should yield not less than 16% of volatile oil. Flos *Caryophylli*, *P. Helv. V*, should yield not less than 16% of essential oil; ash, not more than 7%; acid-insoluble ash, not more than 1%.

The Food and Drug Administration of the U.S. Dept. of Agriculture defines cloves as the dried flower-buds of *Caryophyllus aromaticus* L. Contains not more than 5% of clove stems, not less than 15% of volatile ether extract, not less than 12% of quercitannic acid, not more than 10% of crude fibre, not more than 7% of total ash, and not more than 0.5% of ash insoluble in hydrochloric acid.—*S.R.A., F.D., No. 2, Rev. 4, Aug. 1933*.

The export of cloves from Zanzibar is controlled by a Clove Growers Association. There are standards for three different grades and each bale or package must be up to the standard for the particular grade.—*Perfum. essent. Oil Rec., 1934, 239*.

Oleum Caryophylli (*B.P. '32*). By difference from the volume of the oil unabsorbed by potassium hydroxide solution, a eugenol content of not less than 85% and not more than 90% *v/v* should be indicated. Sp. gr., 1.047 to 1.060. n_{D20} , 1.528 to 1.537. Soluble in 2 volumes of alcohol (70% sp. gr. 0.8896 to 0.8901). *Oleum Caryophylli, U.S.P. X*, should contain not less than 82% *v/v* of eugenol, the absorption of the eugenol with potassium hydroxide being effected during 10 minutes at the temperature of the water bath. The optical rotation should not exceed $-1^{\circ}10'$ in a 100 mm. tube at 25°.

Clove oil may contain up to 20% of acetyl-eugenol, which is hydrolysed so easily that it appears as eugenol in the assay for phenols.

Oils having a eugenol content of more than 90% are obtainable but are less fragrant.—C. T. Bennett, *Pharm. J.*, i/1933, 150.

Oil of clove roots. The yield of oil is about 6% from the roots; the eugenol content is high.—*Chem. & Drugg.*, i/1923, 136. Oil distilled from clove stems is also usually high in eugenol.

Eugenol (*B.P.C. '34*). $C_{10}H_{12}O_2 = 164.1$. Sp. gr., 1.072 to 1.074; n_{D20} , 1.541 to 1.542. Eugenol, *U.S.P. X*, has a sp. gr. at 25° of 1.064 to 1.070 and boils between 250° and 255°.

Oleum Myrciæ (*B.P.C. '34*). Contains not less than 45% of phenols. Sp. gr., 0.945 to 0.990; α_D , 0° to -4° ; n_{D20} , 1.500 to 1.520. Estimate by the B.P. method for eugenol in *Oleum Caryophylli*. The *N.F. V* oil should have a rotation not exceeding -3° in a 100 mm. tube at 25°; sp. gr., 0.962 to 0.990 at 25°.

For an account of the cultivation and distillation in the West Indies, see *Perfum. essent. Oil Rec.*, 1927, 64.

An oil obtained from *Pimenta acris* var. *citrifolia*, lemon-scented bay oil, contains citral 44% and phenols 10%; it has a lemon-like odour.—*Perfum. essent. Oil Rec.*, 1909, 69. Anise-scented bay oil, from a tree which does not seem to have been botanically distinguished from the above, contains a low proportion of eugenol, comparatively large quantities of estragol (15%) and methyl eugenol (13%). For the causes of variation in commercial oil of *Pimenta acris*, see *Yearb. Pharm.*, 1919, 75; also *Perfum. essent. Oil Rec.*, 1927, 343.

Pimenta (*B.P.C. '34*). Yields not more than 6% of ash.

The Food and Drug Administration of the U.S. Dept. of Agriculture defines allspice, pimento, as the dried, nearly ripe fruit of *Pimenta officinalis* Lindl. Contains not less than 8% of quercitannic acid, not more than 25% of crude fibre, not more than 6% of total ash or more than 0.4% of ash insoluble in hydrochloric acid.—*S.R.A., F.D., No. 2, Rev. 4, Aug. 1933*.

Oleum Pimentæ (*B.P.C. '34*). Eugenol content, determined as for *Oleum Caryophylli*, not less than 60% *v/v*; sp. gr., 1.035 to 1.057; α_D , 0° to -5° ; n_{D20} , 1.500 to 1.536. *Oleum Pimentæ, N.F. V*, should contain 65% *v/v* of eugenol. Sp. gr. at 25°, 1.018 to 1.048; n_{D25} , 0° to -4° .

CASCARA SAGRADA

Cascara Sagrada (B.P. '32). Foreign organic matter, not more than 2%. Ash, not more than 6%.

Substitutes. The bark from Texas, Arizona, Colorado, and New Mexico is sometimes substituted by or mixed with the bark of *Rhamnus Californica*, which is of a greyer tint externally, and the transverse section is less dark and more yellow than *R. Purshiana*. An inferior variety, known as Winter Bark, is cut from the steamed branches and is therefore in the form of chips.—*Chem. & Drugg.*, i/1925, 560.

Extracts of the wood were found to be 71% as effective as those from bark. Only some of the trees gave an extract with griping properties. This was improved by oxidation with hydrogen peroxide. (The action of H_2O_2 said to be equivalent to the customary 3 years' storage.—*Pharm. J.*, i/1924, 41.)

Total solids for bark extract 27.4%, and for wood 4.69%. It is a commercial proposition, if the liquid extracts of the wood were made two or three times as concentrated as those from bark.—R. H. Clark and K. R. Gillie, *Vancouver Med. Assn. Bulletin*, Oct. 1925.

Cultivation in British Isles. Trials have been made at various stations. About 35% of the seeds planted in 1908 were fertile. The seeds should be removed from the stiff pulp (dried fruit). Seems to prefer light to heavy soil. Can be raised by cuttings 3 to 4 inches long. Bark should be removed between end of May and end of August.

Scottish soil and climate quite suitable for growing the trees.—A. McCutcheon, *Pharm. J.*, i/1921, 72; *Chem. & Drugg.*, i/1921, 151.

The names BARBERRY and BEARBERRY, misapplied to cascara, have caused confusion in the States of Washington and Oregon and in British Columbia. Genuine cascara grows usually with Red Alder (*Alnus rubra*), the Giant Cedar (*Thuja plicata*) and the Douglas Fir (*Pseudotsuga mucronata*).—*Pharm. J.*, i/1924, 530.

The actual purgative body in cascara is unknown. Tschirch isolated a principle, anthra-gluco-sagradin, and similar principles from rhubarb, senna and rhamnus.

Oxymethylantraquinones are characteristic constituents of purgative drugs from widely separated natural orders, e.g., rhamnus (*Rhamnaceæ*), cassia (*Leguminosæ*), quassia (*Simarubaceæ*), aloe (*Liliaceæ*).

The larger proportion of anthraquinone derivatives in cascara are in the combined form. The U.S.P. fluid extract contained 0.4%. Fluid extracts of commerce contained 0.17% and 0.24%. Debittered cascara contained 0.07%.—*J. Amer. Pharm. Ass.*, 1926, 847.

The characteristic aperient action is not due to emodin. Emodin is, however, a constituent, but chrysophanic acid or chrysarobin could not be found. Apparently there are no chemical differences between one and three years' old ("matured") bark. Storage was said to exhaust a ferment and to moderate the griping action which the fresh bark possesses.

No relation between the emodin content and the physiological action.—J. D. v. d. Graaf, *Pharm. Weekbl.*, 1932, 753.

CERA ALBA

Cera Alba (B.P. '32). Acid value, 18 to 24; the wax complies with the other constants and tests for Cera Flava. Cera Alba, U.S.P. X, has an acid value of 17 to 23, an ester value of 72 to 79, and responds to the other tests for Cera Flava, U.S.P. X.

Cera Flava (B.P. '32). Sp. gr., 0.958 to 0.970; m.p., 62° to 64°; n_{D80° , 1.4380 to 1.4420. Acid value, by titration in absolute alcohol with N/2 alcoholic potassium hydroxide, 17 to 23. Ester value, 70 to 80. Ratio number, 3.3 to 4.0. Cera Flava, U.S.P. X, has an acid number of 18 to 24, and an ester number of 72 to 77.

Cetaceum (*B.P.C.* '34). M.p., 42° to 50°; n_{D80° , about 1.4330. Acid value, not more than 1.0. Saponification value, 120 to 136. Iodine value, to 4.4. Cetaceum, *U.S.P. X*, has a sp. gr. of 0.938 to 0.944, determined by the sp. gr. of the alcohol-water mixture in which globules of wax float and rise indifferently. M.p., 42° to 50°.

Oleum Theobromatis (*B.P.* '32). M.p., 30° to 35°. n_{D40° , 1.45 to 1.4575. Acid value, not more than 4.0. Saponification value, 188 to 192. Iodine value, 35 to 40. The *U.S.P. X* specifies a refractive index at 40° of 1.45 to 1.4578 and an iodine value of 33 to 38. (The m.p. and saponification value limits are the same as the *B.P.* '32.)

Genuine cocoa-butter extracted from five varieties of cocoa had a "crystallisation temperature" of 20.0°; Borneo tallow has a "crystallisation temperature" of about 31.3° and the presence of the latter in cocoa-butter can be shown by means of a special apparatus devised for determining this factor.—S. A. Ashmore *Analyst*, 1934, 515.

CHLORAMINA

Chloramina (*B.P.* '32). $C_7H_7O_2NClSNa, 3H_2O = 281$. Contains from 98% to the equivalent of 103% of the pure hydrate compound. Assayed by interaction with potassium iodide in acidified solution for 10 minutes, followed by titration of the liberated iodine with sodium thiosulphate; 1 ml. of N/10 thiosulphate is equivalent to 0.01408 g. of $C_7H_7O_2NClSNa, 3H_2O$. Chloramina, *U.S.P. X*, should contain from 11.5% to 13% of active chlorine, assayed by digestion with potassium iodide in acetic acid solution. 1 ml. of N/10 thiosulphate is equivalent to 0.001773 g. of active chlorine.

The theory appertaining to the use of this substance as an antiseptic is the hypochlorous acid acting on protein and allied bodies containing the $>N$ group effects a substitution of the H atom by Cl with formation of chloramine. These chloramines in themselves are all potent antiseptics, and bodies of this type are formed in wounds when treated with hypochlorite antiseptics. A soluble chloramine compound was looked for, which led to the selection of *p*-toluene-sodium-sulphonechloramide and the benzene analogue, both of which can be used in higher concentration than the hypochlorites. The simplest chloramine, NH_2Cl , is probably formed during treatment of sewage by hypochlorite.—H. D. Dakin, *Brit. med. J.*, ii/1915, 318, 810.

Bactericidal Power. Chloramine - T, 1:1,000,000 in water, after 2 hours' contact kills staphylococci, and in the presence of serum the strength for this and the benzene analogue required is between 1:1500 and 1:250. The benzene analogue is only half as active in water as the "T" body—1:500,000 being required. In concentration below 1 in 10,000,000 the toluene body kills *B. perfringens* in water in 2 hours.—*Brit. med. J.*, ii/1915, 262.

Molecule for molecule it is thought to be 4 times as active as sodium hypochlorite. Almost all the aromatic bodies containing the NCl group are active bactericides. More than one NCl group in the molecule does not increase power.—*Brit. med. J.*, i/1916, 388.

Germicidal power of chlorine antiseptics (chloramine-T, etc.) as compared with acriflavine, etc. The former are far more potent (in the presence of serum). The technique employed by Browning gave misleading data.—H. Dakin and G. K. Dunham, *Brit. med. J.*, ii/1917, 641.

"Activin." Under this name chloramine-T suggested as a general bleaching agent, and suitable for laundries—more effective and less destructive to fabrics than sodium perborate, although less active than the hypochlorites.—*Nature, Lond.*, ii/1924, 625.

Chloramine-T has been suggested to replace the more expensive iodine solution in analytical processes.—*J. chem. Soc. Abstr.*, ii/1925, 66.

Carbasus Chloraminæ (*B.P.C.* '34). Contains from 4% to 6% $C_7H_7O_2NClSNa, 3H_2O$.

Dichloramina (*B.P.C.* '34). $C_7H_7O_2NCl_2S = 240.0$. Determined by titration of the iodine liberated from potassium iodide in acetic acid solution, it contains not less than 93% of $C_7H_7O_2NCl_2S$; 1 ml. of N/10 thiosulphate is equivalent to 0.006001 g. of $C_7H_7O_2NCl_2S$. The *U.S.P.* X substance should contain not less than 28% and not more than 30% of active chlorine.

CHLOROFORMUM

Chloroformum (*B.P.* '32). $CHCl_3 = 119.4$. Sp. gr., 1.485 to 1.490. Usually not more than 15% *v/v* distils below 60°, the remainder distilling between 60° and 62°. Limit of residue on evaporation, 0.004% *w/v*. Tests for acidity, chloride, free chlorine, hydrochloric acid, foreign organic matter, foreign chlorine compounds, decomposition products and aldehyde are included. Chloroformum, *U.S.P.* X, leaves not more than 0.002% *w/v* of residue, dried at 100°; it contains from 99% to 99.5% of $CHCl_3$. Sp. gr. at 25°, 1.474 to 1.478. Chloroformum ad narcosin, *P. Helv.* V, is required to be of a higher degree of purity than Chloroformum which is administered in solution; two independent series of control tests are prescribed for these substances.

Determination. Colorimetric determination of small quantities in solution (0.1% to 0.0001%) in animal tissues. A pink colour is obtained on heating a solution with pyridine in presence of sodium hydroxide.—W. H. Cole, *J. Biol. Chem.*, 1926, 71, 173.

Chloroform in various mixtures and galenicals may be determined colorimetrically by means of the colour reaction that it gives with β -naphthol in strong potassium hydroxide solution. 10 ml. of 2% *w/v* solution of β -naphthol in 40% cold potassium hydroxide solution is measured in a series of Nessler tubes, measured volumes of a 0.5% standard solution of chloroform in 95% industrial methylated spirit, and sufficient industrial methylated spirit to make the total volume measure 11 ml. are added; the tubes are shaken and allowed to stand for 5 to 10 minutes, and the colours compared by means of a Duboscq colorimeter. If the colours are compared within a few minutes, good results are obtained.—W. G. Moffitt, *Analyst*, 1933, 2.

Test showing presence of 1 part per million of phosgene. To 15 ml. of medicinal chloroform (which contains alcohol) in a dry stoppered bottle add 10 mg. each of resorcinol and vanillin. Close the bottle and, when the reagents are dissolved, place it in the dark for 1 hour. Add 5 ml. of 1% aqueous ammonia, shake, and allow to separate. In presence of phosgene or hydrochloric acid a pink or red colour develops in the aqueous layer, reaching a maximum in 30 seconds.—N. L. Allport, *Analyst*, 1931, 706.

Historical. Discovered by Soubeiran in 1831, named by Liebig trichloride of formyle (1832) and re-named chloroform by Dumas in 1834. The discovery of the anæsthetic effect of chloroform when inhaled by human beings is usually ascribed to Sir J. T. Simpson, who tried it upon himself on Nov. 4, 1847. Its anæsthetic properties were, however, suggested to Simpson by David Waldie of the Liverpool Apothecaries' Hall, and had been previously tested by Dr. Matthews Duncan, Simpson's assistant. Chloric ether (spirit of chloroform) had been used as an anæsthetic at St. Bartholomew's Hospital in the previous March.—J. P. Gilmour, *Quart. J. Pharm.*, 1934, 440.

Trichlorethylene. A British Standard Specification (*B.S.S. No.* 580—1934) has been issued by the British Standards Institution for trichlorethylene (technical and stabilised). The specification includes requirements regarding description, specific gravity (1.469 to 1.475 at 15.5°), distillation range, residue on evaporation, acidity, free chlorine and sampling, and the appendices describe the methods and apparatus to be used.

Carbonei Tetrachloridum (*B.P.* '32). $CCl_4 = 153.8$. Sp. gr., 1.603 to 1.606; boiling-range, 76.5° to 77.5°. Residue on evaporation on a water-bath, not more than 0.002% *w/w*. The *U.S.P.* X substance after evaporating nearly

to dryness on a water-bath and then spontaneously followed by drying at 100° leaves not more than 0.002% *w/v* of residue.

A British Standard Specification (*B.S.S. No. 575—1934*) has been issued by the British Standards Institution for carbon tetrachloride. The specification includes requirements regarding description, specific gravity, distillation-range, residue on evaporation, acidity, oxidisable impurities, free chlorine, sulphur compounds and sampling, and the appendices describe the methods and apparatus to be used.

The proportion of carbon disulphide in benzene, carbon tetrachloride and other liquids can be found colorimetrically by means of diethylamine and a copper salt. One part in 1,000,000 parts of benzene can be detected.—T. Callan, J. A. R. Henderson and N. Strafford, *J. Soc. chem. Ind., Lond.*, 1932, 193.

The statement that specimens of carbon tetrachloride contaminated by carbon disulphide are extremely toxic has no scientific authority. There is no sulphur compound known which is lethal to an adult of 60 kilos in doses of 1/40,000 ml. this being the amount of sulphur derivatives present in 5 ml. of carbon tetrachloride purified for internal use, and containing 1 in 200,000 parts of carbon disulphide. The lesions produced by carbon tetrachloride are identical with those produced by other closely allied members of the chlorine substitution products of the aliphatic hydrocarbons, such as chloroform, and are altogether different from those produced by carbon disulphide.—J. W. Tomb, *Brit. med. J.*, i/1934, 1097.

Toxic effects of the carbon tetrachloride group.—Sir W. Willcox, *Brit. med. J.*, i/1934, 105.

Quantitative methods for the determination of chloroform or carbon tetrachloride in mixtures or capsules are described in *Methods of Analysis* (*A.O.A.C.*, 1930, 479).

Hexachlorethane. A British Standard Specification (*B.S.S. No. 577—1934*) has been issued by the British Standards Institution for hexachlorethane. The specification includes requirements regarding description, melting-range (183° to 187°), moisture, matter insoluble in alcohol, ash, acidity and alkalinity, grading and sampling, and the appendices describe the methods and apparatus to be used.

Chloralis Hydras (*B.P. '32*). $\text{CCl}_3 \cdot \text{CH}(\text{OH})_2 = 165.4$. Should contain not less than 99% of the pure substance. Assayed by addition of excess of N/1 sodium hydroxide, standing for 2 minutes, and back titration with N/1 sulphuric acid to phenolphthalein. Ash, not more than 0.05%. The *U.S.P. X* requires a purity of 99.5%.

Chloralformamidum (*B.P.C. '34*). $\text{C}_3\text{H}_4\text{O}_2\text{NCl}_3 = 192.4$. M.p., 114° to 115°. Volatilises without evolving inflammable vapours and leaves not more than 0.01% of residue.

The melting-point of chloral formamide, as given in the *B.P.C. '34*, is not in accordance with experiment. It would more correctly be recorded as 124° to 126° with limits for pharmaceutical purposes between 122° and 126°.—C. T. Bennett and N. R. Campbell, *Quart. J. Pharm.*, 1935, No. 3.

Butylchloralis Hydras (*B.P.C. '34*). $\text{C}_4\text{H}_7\text{O}_2\text{Cl}_3 = 193.4$. Ash, not more than 0.05%. Tests for limit of chloride and of chloral hydrate are described.

Chlorbutol (*B.P. '32*). $\text{C}_4\text{H}_7\text{OCl}_3 = 177.4$. M.p., not below 78°. M.p. of the anhydrous substance, 96°. Ash, not more than 0.1%. The majority of samples melt slightly below the *B.P.* minimum.

Alcohol trichlorisobutylicus, *P. Helv. V*, is $\text{C}_4\text{H}_7\text{OCl}_3, \frac{1}{2}\text{H}_2\text{O}$, and, without previous drying, melts between 79.5° and 81°. It is assayed as follows:—Dissolve about 1 g. in 20 ml. of alcohol and dilute to 100 ml. with water. Transfer 10 ml. to a 200 ml. flask, add 0.5 ml. of 30% sodium hydroxide solution, 10 ml. of alcohol and heat on a water-bath just to boiling. Allow to cool, add 0.5 ml. of concentrated nitric acid, dilute with 50 ml. of water, neutralise with excess of calcium carbonate and titrate the mixture to potassium chromate with N/10 silver nitrate. A blank experiment is also prescribed. Each ml. of N/1 silver nitrate is equivalent to 0.0062147 g. of $\text{C}_4\text{H}_7\text{OCl}_3, \frac{1}{2}\text{H}_2\text{O}$.

Iodoformum (*B.P. '32*). $\text{CHI}_3 = 393.8$. Should contain 99% of CHI_3 . Assayed by digestion overnight with alcohol (95%), N/10 silver nitrate and nitric acid, dilution, and back titration with N/10 ammonium thiocyanate. M.p., 120° to 122°. Ash limit, 0.2%. The *U.S.P. X* specifies that Iodoformum should

not more than 1% on drying over sulphuric acid for 24 hours, and leave not more than 0.2% of ash.

Clark's Assay Process is a very much quicker one than that of the *B.P.*—5 g. of iodoform is dissolved in 50 ml. of methylated spirit and 50 ml. of N/10 silver nitrate is added, followed by 5 ml. of nitric acid; the mixture is boiled under a reflux condenser for at least thirty minutes, cooled, diluted with 100 ml. of water, and titrated with N/10 thiocyanate.—Norman Glass, *Quart. Pharm.*, 1935, No. 3.

Carbasus Iodoformi (*B.P.C.* '34). The iodoform, extracted with alcohol and titrated as Iodoformum, should be equivalent to from 4% to 6%.

CHROMII TRIOXIDUM

Chromii Trioxidum (*B.P.* '32). $\text{CrO}_3 = 100.0$. Contains not less than 95% of CrO_3 . Determined by oxidation of potassium iodide in solution, acidified with dilute sulphuric acid, and titration with N/10 sodium thiosulphate, using starch mucilage as indicator. Water-soluble matter after ignition, not more than 2%. The *U.S.P. X* fixes the same purity, using hydrochloric acid to acidify the titration liquid.

Potassii Dichromas (*B.P.C.* '34). $\text{K}_2\text{Cr}_2\text{O}_7 = 294.2$. Assayed with potassium iodide and N/10 sodium thiosulphate, it contains not less than 99% of pure salt.

CINCHONA

Cinchona (*B.P.* '32). Contains not more than 2% of other organic matter, and not less than 6% of total alkaloids of which not less than one half is quinine and cinchonidine. Ash, not more than 4%. *Assay* (*B.P.* '32 process): The powdered bark is mixed with strong solution of lead subacetate and water and allowed to stand; after standing with ammoniacal alcohol, it is subjected to continuous extraction with more ammoniacal alcohol; the alcohol is recovered, and the residue treated with successive portions of sulphuric acid and water until completely extracted; the filtered aqueous shakings, cleaned by shaking with chloroform, are made alkaline with ammonia and the alkaloid extracted with chloroform, dried at 100° and weighed. The total alkaloids are then dissolved in water, N/1 sulphuric acid and alcohol, and the boiling liquid made just pink to hæmatoxylin with N/10 sodium hydroxide. The acidified and filtered boiling liquid is concentrated, sodium potassium tartrate added, and set aside for 24 hours to crystallise; the alkaloidal tartrates are decomposed with sodium hydroxide and finally extracted with chloroform, evaporated, and the residue of quinine and cinchonidine dried at 100° and weighed. Cinchona, *U.S.P. X*, should contain not less than 5% of alkaloids, determined by heating with hydrochloric acid and water, cooling, macerating with ether, chloroform and water; and finally extracting an aliquot part, made ammoniacal, with chloroform.

Cortex Chinæ, *P.G. VI*, is the bark of *Cinchona succirubra* Pavon, and should yield not less than 6.5% of alkaloid by the process prescribed. **Cortex Cinchonæ**, *P. Helv. V*, is the bark of

cultivated *Cinchona succirubra* Pavon, containing not less than 6.5% of alkaloids; and yields not more than 6% of ash and not less than 15% of water-soluble extractive.

Percolation of a moderately fine powder (44/85) gave better extraction of both alkaloids and total solids, when compared with percolation of either fine powder (85) or a moderately coarse powder (22/60). This indicates that an optimum degree of comminution exists for percolation of cinchona. The relative percentage of alkaloids to other solids increases in successive fractions of percolate.—A. W. Bull, *Quart. J. Pharm.*, 1935, No. 3.

For a comparison of the results given by the *B.P.* assay process with those given by the methods of some other pharmacopœias see P. A. W. Self and C. E. Corfield, *Quart. J. Pharm.*, 1930, 410. The *B.P.* assay processes for cinchona galenicals are based on a further paper by the same authors (*Quart. J. Pharm.*, 1931, 335).

Quantitative methods for the determination of quinine, cinchonine and quinidine are described in *Methods of Analysis (A.O.A.C., 1930, 452)*.

Alpha-Naphthol Test for Cinchona Alkaloids. Added to an aqueous solution of quinine sulphate, a few drops of fresh saturated alcoholic alpha-naphthol solution to which a few drops of concentrated sulphuric acid (2 drops per ml.) have been added, produce a yellow precipitate; when the reagent is in excess a yellow solution results. Quinidine, cinchonidine and cinchonine sulphates act likewise; no other white alkaloids appear to give this reaction. Cinchona alkaloids can thus be detected in presence of atropine, morphine, cocaine, strychnine, caffeine, brucine, codeine and antipyrine. A drop of the reagent added to chloroform or ether residues of any of the cinchona alkaloids gives a yellow colour.—Watson, *Amer. J. Pharm.*, 1913, 502; *Pharm. J.* ii/1913, 881.

"Grey" cinchona bark from Huanuco found to contain quinine 0.45%, cinchonidine 0.22%, cinchonine 0.63%, amorphous alkaloid 0.48%.

A further sample of S. American bark contained 5.49% of cinchonine and only 0.027% of quinine. It consisted of *C. nitida* and other varieties, and was also "grey" bark. The abnormal content of cinchonine probably due to cultivation or growth at low altitudes and in hot moist atmosphere.—B. F. Howard and O. Chick, *Yearb. Pharm.*, 1920, 385.

Approximate determination as used by the planters for *C. Ledgeriana*. Extract with ether, using slaked lime and sodium hydroxide. Dissolve residue in ether and N/HCl, and titrate with N/NaOH, using litmus. Precipitate tartrate of quinine and cinchonidine, filter, wash, dry and weigh. Determine optical rotation, α , and calculate quantity of quinine and cinchonidine from Cammell's table. To the filtrate from the tartrates add NaI solution to precipitate quinidine, cinchonine and amorphous alkaloids. Separate quinidine with 94% alcohol.—*Yearb. Pharm.*, 1923, 8.

History and Development of the Cinchona Plant. The cultivation of the cinchonas is carried on in India, in the Nilgiri Hills in the south, and near Darjeeling in the north-east, also in Ceylon, Java, and Jamaica. A good résumé was given in a paper communicated by Lt.-Col. A. T. Page (late I.M.S.) to the Royal Society of Tropical Medicine and Hygiene, London, Jan., 1925.

After reviewing the various factors which led to the cultivation of cinchona in Java, Ceylon and India, attention was drawn to the trial in India, in 1873, of cinchona febrifuge (then a mixture of the total alkaloids of *C. succirubra*) and the report of the Surgeon-General of that year of its efficacy in malaria, its low price and its ease of manufacture. The high market price of quinine naturally resulted in the planting of more *C. Ledgeriana* trees, and so, in 1903, the composition of the febrifuge consisted of a mixture of the residual alkaloids after extraction of quinine, from the barks of *C. Ledgeriana* and *C. succirubra*, with a certain amount of added quinine, to make it similar to the original. In spite of this the quantity manufactured rapidly declined, and with the advent of the war the demand exceeded the possible supply, and the price naturally increased. This has resulted in the inability of the vast multitude of natives who are in continuous residence in mosquito-infested districts, to procure the necessary treatment, and for them, in the absence of conclusive proof that one alkaloid or combination of alkaloids is far superior to all others, the fittest product is the one which can be produced and distributed at the least possible cost and can be used with the least supervision. It seems, therefore, that although

inine has been proved to be the fittest separated alkaloid, some supplementation of it is indicated. This could be achieved most easily and cheaply by reverting to the cultivation of *C. succirubra*, and the extraction of its total alkaloids to form again the original cinchona febrifuge.

It has not been recognised that there are two factories in India, and that, while in Bengal we grow our own bark which contains much quinidine, the Madras factory has lately had to depend largely on Java bark, and that therefore our cinchona febrifuges are different.—G. E. Shaw, Streatfeild Memorial Lecture, 1934.

A very interesting account of the introduction of cinchona cultivation from Peru into India and the cultivation of *C. Calisaya* (from the seed of a native Indian tree) in Java in 1852 by the Dutch. They realised their mistake, however, in 1861, and started cultivation, but it was badly managed. In 1916 the Great War showed the error of allowing a friendly neutral to have monopoly in a bark rich in quinine. Attention is again drawn to Maj. Acton's work showing that total alkaloids are as good as quinine, and that Indian bark supplies an equivalent amount of these. It was bark and not quinine that started the fame of cinchona from Peru.—*Chem. & Drugg.*, ii/1920, 1447.

History of cinchona. Varieties to grow for profit.—Sir David Prain, *Brit. med. J.*, ii/1925, 963.

Java now grows well over 90% of the world's production of cinchona. Nearly all that grown in India is *C. Ledgeriana*, partly hybridised with *Calisaya*. Some *officinalis* and a little *succirubra* and the hybrid between *Ledgeriana* and *succirubra* are grown, but the proportion is very small. In 1905, the bark being harvested contained an average of only 1.5% quinine sulphate. Since then the average has been brought up to about 5%. The crude sulphate is dissolved in the minimum quantity of nearly boiling water, filtered and heated for twenty minutes with decolorising carbon, refiltered and allowed to cool. The recrystallisation has to be repeated to obtain a snow-white product with less than 3% of cinchonidine sulphate. There can be no doubt but that the Royal Commission on Agriculture were quite right when they reported, in 1928, that if India is to embark on any large campaign for fighting malaria, the price of quinine must be reduced, that India must be self-supporting, and that therefore extensions of the plantations are necessary.—G. E. Shaw, Streatfeild Memorial Lecture, 1934.

Æthylhydrocupreinæ Hydrochloridum (B.P.C. '34). $C_{21}H_{28}O_2N_2 \cdot HCl = 376.7$. By extraction with chloroform from ammoniacal solution, evaporation, and drying at 100° , it contains not less than 90% of $C_{21}H_{28}O_2N_2$. Æthylhydrocupreinum basicum and Æthylhydrocupreinum hydrochloridum are official in the *P. Helv. V* and each contains not less than 99% of the pure substance.

Cinchonidinæ Sulphas (B.P.C. '34) $(C_{19}H_{22}ON_2)_2 \cdot H_2SO_4 \cdot 7H_2O = 812.6$. Loss at 100° , not more than 16%. Ash, not more than 0.1%. A limit test for quinine, cinchonine and quinidine is described. The official salt of the *U.S.P. X* is the trihydrate which should lose not more than 12% at 100° .

Cinchonidine sulphate, though very soluble, forms a double compound with quinine sulphate and so always crystallises with the quinine to some extent.—G. E. Shaw, Streatfeild Memorial Lecture, 1934.

Cinchoninæ Hydrochloridum (B.P.C. '34). $C_{19}H_{22}ON_2 \cdot HCl \cdot 2H_2O = 366.7$. Loss at 100° , not more than 10%. Ash limit, 0.1%.

Quinetum (B.P.C. '34). Yields not less than 60% of quinine and cinchonidine, and loses not more than 5% at 100° . Ash, not more than 1%. Assayed by the *B.P.* method for Totaquina.

The Malaria Commission of the League of Nations recommended (1932) that quininetum should be the name applied to a mixture of quinine, cinchonidine and cinchonine in equal parts, this being approximately the proportion in which the alkaloids occur in *Cinchona succirubra*. Of three commercial samples, only one met this specification.—J. A. Goodson and T. A. Henry, *Quart. J. Pharm.*, 1932, 161.

Totaquina (B.P. '32). Should contain not less than 70% of crystallisable alkaloids of which at least one-fifth is quinine. On drying for one hour at 70° and then at 100° , the loss is not more than 5%. Ash, not more than 5%. *Assay* (*B.P.* '32 process): a boiling solution of 2 g. in 20 ml. of N/1 sulphuric acid,

40 ml. of water and 40 ml. of 95% alcohol, made just alkaline to litmus with N/10 sodium hydroxide, is cooled and made just acid, boiled and filtered; the filtrate is evaporated to 120 g., 30 g. of sodium potassium tartrate added and stood for 24 hours. The precipitate, collected on a hardened filter, is washed with 80 ml. of 25% sodium potassium tartrate solution, decomposed with sodium hydroxide and extracted with chloroform; the proportion of quinine in this residue of quinine and cinchonidine is estimated by a methoxyl determination, by interaction with hydriodic acid, passing the methyl iodide into silver nitrate and weighing as AgI. The filtrate and washings from the precipitate and tartrate are made alkaline with sodium hydroxide and extracted with ether; the alkaloid transferred to acid and the cinchonine precipitated by running into ether and N/1 sodium hydroxide; the precipitate, collected on a weighed filter, is washed with the ether from the filtrate and with two further ether shakings of the aqueous solution, and finally dried at 100°, adding a correction for solubility in ether. The separated ethereal layer of the filtrate is extracted with 10% w/w solution of glacial acetic acid, the boiling solution neutralised with dilute ammonia, 5 g. of potassium iodide added and stood overnight. The precipitate, washed with 50% alcohol, is dried at 100°, weighed as quinidine hydriodide and corrected for loss due to solubility.

Alternative assay processes for Totaquina Type I (made direct from the bark of *C. succirubra*) and Type II (made from residues of quinine extraction and adjusted by the addition of quinine) are described.—*Quart. Bull. Hlt. Org. L. o. N.*, 1934, 3, 339.

Quinidina (*B.P.C.* '34). $C_{20}H_{24}O_2N_2 \cdot 2H_2O = 360 \cdot 2$. Loss at 100°, not more than 10%. Ash, not more than 0.1%.

Quinidinæ Sulphas (*B.P.* '32). $(C_{20}H_{24}O_2N_2)_2 \cdot H_2SO_4 \cdot 2H_2O = 782 \cdot 5$. Loss at 100°, not more than 5%. Ash, not more than 0.04%. It is tested for other cinchona alkaloids by precipitating as iodide and adding ammonia to the filtrate, when no turbidity should be produced. The *U.S.P.* X allows the same moisture limit and 0.1% of ash.

Chinidinum sulfuricum, *P. Helv. V*, should contain 99.5% of $(C_{20}H_{24}O_2N_2)_2 \cdot H_2SO_4 \cdot 2H_2O$. Other cinchona alkaloids are excluded by the following tests:—(a) Dissolve 5 g. of quinidine sulphate in 10 ml. of water, add 0.5 g. of potassium iodide and maintain the liquid for 1 hour at 15°, shaking strongly and frequently; filter through a glass filter and add 2 drops of 3.4% w/v solution of ammonia; no cloudiness should be produced either immediately or within 1 hour. (b) The rotation of a solution of 0.391 g. in 0.8 ml. of 7.3% w/v hydrochloric acid and 20 ml. of water, at 20° and in a 200 mm. tube, should be between +10.5° and +10.7°.

Mechanism of death from quinidine. Cat experiments showed that the m.l.d. of quinidine bisulphate is dependent on the speed of administration; e.g., 25 mg. per kilo is usually fatal in a single dose, but with a smaller dose given at 6, 12, or 24-minute intervals the total m.l.d. increased to 0.1 g. per kilo. Striking fall in blood pressure immediately following injection of non-lethal doses.—B. Gordon and co-workers, *J. clin. Invest.*, Aug. 1925, per *J. Amer. med. Ass.*, ii/1925, 1162.

QUININE AND ITS SALTS

The following table shows the principal *B.P.* and *B.P.C.* standards for quinine and the salts of quinine. All, with the exception of Quininæ æthylis Carbonas, are required to comply with the *B.P.* '32 test for limit of other cinchona alkaloids. The quantities which are directed to be taken for the test are given in the fourth column of the table. The specified quantity of the substance with 50 ml. of water and 5 ml. of dilute sulphuric acid is made ammoniacal with 5 ml. of dilute solution of ammonia and extracted with 30 ml. and then 20 ml. of chloroform, each being washed with two 10 ml. quantities of water; most of the chloroform is evaporated, about 3 ml. of dehydrated alcohol added and quickly evaporated. The opaque residue is dissolved in 20 ml. of alcohol and 20 ml. of water, and 1 ml. of a methyl red solution added; at 75° the solution is adjusted with N/5 sulphuric acid to the same colour as 56 ml. of solution of pH 5.44 at 20°, with 1 ml. of the methyl red solution; the mixture is evaporated to dryness on a water-bath and powdered, 1 g. boiled with 30 ml. of water under a reflux condenser, is cooled rapidly to 15°, shaking vigorously and maintained at that temperature, with frequent shaking, for 30 minutes and filtered rapidly. 6.5 ml. of solution of ammonia (10.0% to 10.2% w/w NH₃) at 15° is added all at once to 5 ml. of the clear filtrate at 15° and on mixing gent

a clear liquid should be produced. Quininæ Tannas is extracted, before applying this test, with ether from a sodium hydroxide, ether and tragacanth mixture, the ethereal liquid being then extracted with sulphuric acid.

Chininum sulfuricum, *P. Helv. V*, is the stable dihydrate, $(C_{20}H_{24}O_2N_2)_2 \cdot H_2SO_4 \cdot 2H_2O$, and contains from 4.5% to 4.7% of water. The absence of other cinchona alkaloids is ensured by the following tests:—(a) Dissolve 0.85 g. of the quinine sulphate in 50 ml. of boiling water in a tared flask; cool rapidly and shake well, and make up to 51 g. with water; add 5 g. of powdered potassium sulphate and keep at 20° for 30 minutes, shaking frequently and strongly. Filter through a porous glass filter, mix 20 ml. of the filtrate with 6.0 ml. of water, add 1 drop of 8.5% *w/v* sodium hydroxide solution and shake vigorously. No turbidity is produced immediately or within one minute. (b) The rotation of a solution of 0.746 g. in 1 ml. of 9.8% *w/v* sulphuric acid and 1 ml. of 7.3% *w/v* hydrochloric acid with sufficient water to make 20 ml., at 20° and in a 200 mm. tube, should be between -17.8° and -18° .

Quininæ et Æthylis Carbonas (*B.P.* '32). It is impossible to obtain a product complying with the *B.P.* requirement that the melting-point should not be below 95°. Practically all commercial samples have a melting-point of about 89° to 91° after drying over sulphuric acid, but it is difficult to obtain consistent results unless a standard method of procedure is adopted.

The melting-point of quinine ethyl carbonate given in the *B.P.* appears to be too high. The melting point of the dried salt of pharmacopœial purity seems to lie between 90° and 92°. When the salt is purified by recrystallisation the melting-point may be raised to 91.5° to 92.5°.—G. R. Page, *Quart. J. Pharm.*, 1934, 361.

Nephelometric estimation of quinine in blood and urine after administration in treatment, employing Tanret's reagent. The ether used is purified so that it gives no reaction for aldehydes with Schiff's reagent or for ketones with Scott Wilson's reagent, *q.v.* No turbidity must develop on shaking the ether with excess of the reagent.—I. J. Lipkin and W. Ramsden, *Brit. med. J.*, i/1918, 560.

As native patients may omit to take their quinine, test the urine with a few drops of Mayer's reagent: a white precipitate appears if quinine is present. To distinguish from albumin, heat the upper part of the test-tube—if caused by albumin the cloud becomes more dense, but if by quinine it disappears when the liquid boils.—per *J. trop. Med. (Hyg.)*, May 1, 1928, 105.

Tanret's Reagent. Potassium iodide 3.32 g., mercuric chloride 1.35 g., acetic acid 20 ml., diluted with distilled water to 60 ml. Precipitates alkaloids and albumin. Better than Mayer's for quinine test in urine, providing urine is albumin-free.

Bromophenol Blue is a good indicator for titrating neutral quinine salts.—N. Evers, *Pharm. J.*, i/1921, 470.

The optimum titration conditions for the cinchona alkaloids, with advice on selection of indicators.—C. Morton, *Yearb. Pharm.*, 1926, 447.

A paper dealing with the clinical aspects of the use of cinchona and its alkaloids in malaria was read by Lt.-Col. Clayton Lane (late I.M.S.), before the Roy. Soc. Trop. Med. Hyg., London, in Jan. 1925. The action of quinine in combating the malarial parasite is accomplished, either directly by the quinine, or by a metabolite formed by, or from, it; if the former, the greater its concentration in the blood, the better; if the latter, then the less detectable, the better. Although only a small quantity of quinine is excreted as such, it disappears very rapidly from the blood, as shown by experiments on intravenous injection. Further experiments consisted in the incubation of parasites in a medium containing quinine in a much greater concentration than it would occur therapeutically. The medium, afterwards injected into paralytics, produced malaria, thus suggesting that the alkaloid acts indirectly or through the medium of a metabolite.

Regarding the salt best suited for oral use, it is evident that, as practically no quinine is absorbed by the stomach, whatever salt is given it will be precipitated in the intestine as base. If, however, it is a metabolite which is curative, the salt which most easily admits of intestinal metabolism should be given.

Quinine bisulphate and oxyquinoline sulphate can be, and are, absorbed from the vaginal tract of experimental animals when instilled in aqueous solutions.—D. I. Macht, *J. Pharmacol.*, iii/1928, 145.

Substance	Percentage of Anhydrous Quinine	Maximum % loss on drying	Quantity to be taken in "other cinchona alkaloids" test	Maximum % of ash
Quinina (<i>B.P.C.</i> '34) $C_{20}H_{24}O_2N_2 \cdot 3H_2O = 378.3$	not less than 85	15 at 100°	1.1 g. (in 20 ml. of 90% alcohol commencing with addition of 20 ml. of water and methyl red)	0.05
Quininæ Acetylsalicylas (<i>B.P.C.</i> '34) $C_{20}H_{24}O_2N_2 \cdot C_9H_8O_4 = 504.3$	not less than 63.5	1 at 100°	1.5 g.	0.05
Quininæ Arsenas (<i>B.P.C.</i> '34) $(C_{20}H_{24}O_2N_2)_2 \cdot H_3AsO_4 \cdot 8H_2O = 934.5$	not less than 69	16 at 100°	1.4 g.	—
Quininæ Benzoas (<i>B.P.C.</i> '34) $C_{20}H_{24}O_2N_2 \cdot C_7H_6O_2 = 446.3$	72 to 75	—	1.4 g.	0.1
Quininæ Bisulphas (<i>B.P.</i> '32) $C_{20}H_{24}O_2N_2 \cdot H_2SO_4 \cdot 7H_2O = 548.4$	about 59	24 at 110°	1.7 g. (in 50 ml. water without addition of acid)	0.04
Quininæ Citras (<i>B.P.C.</i> '34) $(C_{20}H_{24}O_2N_2)_3 \cdot C_6H_8O_7 \cdot 7\frac{1}{2}H_2O = 1300$	not less than 74.5	10.5 at 100°	1.3 g.	0.1
Quininæ Dihydrobromidum (<i>B.P.C.</i> '34) $C_{20}H_{24}O_2N_2 \cdot 2HBr \cdot 3H_2O = 540.1$	not less than 59	11 at 100°	1.7 g.	0.1
Quininæ Dihydrochloridum (<i>B.P.</i> '32) $C_{20}H_{24}O_2N_2 \cdot 2HCl = 397.1$	about 81	3 at 110°	1.2 g.	0.04
Quininæ Disalicylosalicylas (<i>B.P.C.</i> '34) $C_{20}H_{24}O_2N_2 \cdot C_{28}H_{20}O_{10} = 840.4$	38 to 40	—	2.5 g.	—
Quininæ et Æthylis Carbonas (<i>B.P.</i> '32) $C_{20}H_{23}O_2N_2 \cdot CO_2 \cdot C_2H_5 = 396.2$	—	2 over H_2SO_4 for 24 hours	—	0.04
Quininæ et Ureæ Hydrochloridum (<i>B.P.C.</i> '34) $C_{20}H_{23}O_2N_2 \cdot CH_4N_2O_2 \cdot 2HCl \cdot 5H_2O = 547.3$	not less than 58	16.5 at 100°	1.7 g.	0.1

Substance	Percentage of Anhydrous Quinine	Maximum % loss on drying	Quantity to be taken in "other cinchona alkaloids" test	Maximum % of ash
Quininæ Glycerophosphas (<i>B.P.C.</i> '34) ($C_{20}H_{24}O_2N_2$) ₂ , $C_3H_5O_6P$, $4H_2O$ = 892.6	not less than 70	8.5 at 100°	1.4 g.	—
Quininæ Hydriodidum (<i>B.P.C.</i> '34) $C_{20}H_{24}O_2N_2$, HI = 452.1	not less than 71	1 at 100°	1.4 g.	1.0
Quininæ Hydrobromidum (<i>B.P.C.</i> '34) $C_{20}H_{24}O_2N_2$, HBr, $2H_2O$ = 441.2	not less than 73	9 at 100°	1.3 g.	0.1
Quininæ Hydrochloridum (<i>B.P.</i> '32) $C_{20}H_{24}O_2N_2$, HCl, $2H_2O$ = 396.7	about 82	10 at 110°	1.2 g.	0.04
Quininæ Hypophosphis (<i>B.P.C.</i> '34) $C_{20}H_{24}O_2N_2$, H_3PO_2 , $2H_2O$ = 426.3	not less than 74	9 at 100°	1.3 g.	—
Quininæ Lactas (<i>B.P.C.</i> '34) $C_{20}H_{24}O_2N_2$, $C_3H_5O_3$ = 414.3	not less than 72	3 at 100°	1.3 g.	0.1
Quininæ Phosphas (<i>B.P.C.</i> '34) ($C_{20}H_{24}O_2N_2$) ₃ , $2H_3PO_4$, $6H_2O$ = 1277	74 to 78	10 at 100°	1.3 g.	—
Quininæ Salicylas (<i>B.P.C.</i> '34) $C_{20}H_{24}O_2N_2$, $C_7H_5O_3$, H_2O = 480.3	not less than 67	4 at 100°	1.4 g.	0.1
Quininæ Sulphas (<i>B.P.</i> '32) ($C_{20}H_{24}O_2N_2$) ₂ , H_2SO_4 , $7\frac{1}{2}H_2O$ = 881.6	about 73.5 - 76.5	11 to 16 at 100°	(On the substance dried at 50° for 2 hours commencing with 1 g. boiled with 30 ml. of water)	0.04
Quininæ Tannas (<i>B.P.</i> '32)	30 to 35	10 at 100°	3.3 g. (after preliminary treatment)	0.3
Quininæ Valerianas (<i>B.P.C.</i> '34) $C_{20}H_{24}O_2N_2$, $C_5H_{10}O_2$, H_2O = 444.3	not less than 71	—	1.4 g.	0.1

Growth of Pathogenic Bacteria.—Experiments to determine the effect of certain antiseptics, including quinine and iodine, on the growth of staphylococci and streptococci in the blood, showed that no growth takes place when no quinine is present, but in the presence of one part of quinine in 800 parts of blood copious growth takes place; with iodine, growth increases progressively on raising the concentration of iodine in the blood from 1 : 25,000 to 1 : 400.—Sir A. Wright, *Chem. & Drugg.*, i/1924, 698.

Biological Test for Antimalarial Remedies. Numerous substances have been introduced for the treatment of malaria such as Plasmochin and Atebrin, and their value is determined in the first place by examining their effect in bird malaria.

The method of carrying out the biological test is as follows:—Canaries are infected, the heads of the infected birds are cut off, and the blood is filtered through glass wool into 1% citrate saline, so that the blood becomes diluted 5 or 10 times. This dilution is kept at 37° and injected into normal birds within 25 minutes. The injection is made into the pectoral muscles. If the dilution of blood is not kept at 37° the appearance of parasites is later in those birds which are last inoculated. The average time of the appearance of parasites in untreated birds varies from 4 to 8 days. (See G. A. H. Buttle, T. A. Henry and J. W. Trevan, *Biochem. J.*, 1934, 426.)

To test the efficacy of any unknown preparation, a group of birds is treated with some substance, such as quinine, used as standard, and a second group is treated with the preparation to be tested. The first dose is given about 4 hours after the canary is infected, and subsequent doses once daily for the next five days; the doses are given orally by means of a thin piece of rubber tubing passed down the gullet. The birds are then observed in order to discover how many days elapse before the parasites appear in their blood; the average time for the appearance of parasites in a group of birds which received the same dose is then determined, and the average time for the unknown preparation is compared with the average time for the standard. Thus, a group of six birds which received a total dose of 30 mg. of quinine, reckoned per 20 g. bird weight, showed parasites after an average of 18·2 days, while a group receiving the same dose of dihydrocinchonidine showed parasites after an average of 9·3 days. Thus dihydrocinchonidine is less efficient than quinine in treating bird malaria.

Potassii Hydroxyquinolini Sulphas (*B.P.C.* '34), may be a mixture of 8-hydroxyquinoline sulphate and potassium sulphate or of 8-hydroxyquinoline and potassium acid sulphate. It partly liquefies at 172° to 178° and yields from 30% to 33% of sulphated ash.

Oxychinolinum sulfuricum, *P. Helv. V*, is oxyquinoline sulphate containing not less than 95% of $(C_9H_7ON)_2, H_2SO_4$. It is assayed by dissolving 0·5 g. in 250 ml. of water, mixing 50 ml. of the solution in a closed flask with 25 ml. of dilute hydrochloric acid and 22 ml. of N/10 bromate-bromide solution, and adding 1 g. of potassium iodide after 1 minute. The liberated iodine is then titrated with N/10 sodium thiosulphate in the usual manner and starch is used as indicator. Each ml. of bromate-bromide solution is equivalent to 0·0048525 g. of $(C_9H_7ON)_2, H_2SO_4$.

CINNAMOMUM

Cinnamomum (*B.P.* '32). Ash, not more than 7%. Acid-insoluble ash, not more than 2%. Cinnamomum, *U.S.P. X*, from *Cinnamomum Loureirii* Nees, should yield not less than 2% of volatile ether-soluble extractive.

Cortex Cinnamomi, *P.G. VI*, is required to contain not less than 1% of volatile oil. Cortex Cinnamomi ceylanici, *P. Helv. V*, should yield not less than 1·3% of cinnamic aldehyde when assayed by the following process:—Steam distil a mixture of 6 g. of powdered bark and 100 ml. of water, and treat the first 300 ml. of the distillate with a cold solution of 0·25 g. of semioxamazide in 15 ml. of water; shake well for 10 minutes, and allow to stand for at least 20 hours, agitating the mixture occasionally. Collect the precipitate on a tared Gooch filter dried at 150°, wash the precipitate with

ater, dry for 2 hours at 140° to 150° and weigh after allowing cool over sulphuric acid. The weight of precipitate, multiplied by 10.14, gives the percentage of aldehyde in the bark. Cortex cinnamomi chinensis, *P. Helv. V*, must give not less than 1.5% of cinnamic aldehyde.

The Food and Drug Administration of the U.S. Dept. of Agriculture define cinnamon as the dried bark of cultivated varieties of *Cinnamomum zeylanicum* Nees or of *C. cassia* (L.) Blume. *Ceylon Cinnamon* is the dried, inner bark of cultivated varieties of *Cinnamomum zeylanicum* Nees. *Saigon Cinnamon*, *Cassia*, is the dried bark of cultivated varieties of *Cinnamomum cassia* (L.) Blume. *Ground Cinnamon*, ground cassia, is the powder made from Cinnamon. Contains not more than 5% total ash and not more than 2% ash insoluble in hydrochloric acid.—*S.R.A., F.D., No. 2, Rev. 4, Aug., 1933.*

Oleum Cassiæ (*B.P.C.* '34). From *Cinnamomum Cassia* Blume. Assayed by the *B.P.* method for Oleum Cinnamomi should contain not less than 80% *w/w* of aldehydes as C_9H_8O . Sp. gr., 1.055 to 1.065. $n_{D20^{\circ}}$, 1.600 to 1.606. Soluble in 2 volumes of alcohol (80%, sp. gr. 0.8634 to 0.8640) and 3 volumes of alcohol (70%, sp. gr. 0.8896 to 0.8901).

Imported oil generally contains lead in excess of the *B.P.C.* limit; it is derived from the leaden vessels in which the oil is received.

Direct determination of total aldehydes in cassia oil. For a method which is stated to avoid the error caused in the ordinary process by the too great excess of the bisulphite reagent, see F. D. Dodge, *Amer. Perfum.*, 1929, 24, 11, per *Quart. J. Pharm.*, 1929, 328.

Oleum Cinnamomi (*B.P.* '32). From *Cinnamomum zeylanicum* Nees. Assayed by the *B.P.* method by interaction with hydroxylamine hydrochloride solution and titration with *N/2* potassium hydroxide in 60% alcohol. Cinnamic aldehyde content, 50% to 65% *w/w*. Sp. gr., 1.000 to 1.030. α_D , 0° to -2° . $n_{D20^{\circ}}$, 1.565 to 1.586. Soluble in 3 volumes of 70% alcohol with only a faint opalescence. By the sodium sulphite method used for Oleum Cari, *U.S.P.* X, Oleum Cinnamomi, *U.S.P.* X, obtained from cassia, *Cinnamomum Cassia* (Linné) Blume, contains not less than 70% *v/v* of cinnamic aldehyde.

The Food and Drug Administration of the U.S. Dept. of Agriculture define oil of cinnamon, oil of cassia, oil of cassia cinnamon, for food purposes, as the lead-free volatile oil from the leaves or bark of *Cinnamomum cassia* (L.) Blume; it contains not less than 80% *v/v* of cinnamic aldehyde. *Oil of Ceylon cinnamon*, the lead-free volatile oil from the bark of the Ceylon cinnamon (*Cinnamomum zeylanicum* Nees), contains not less than 65% *w/w* of cinnamic aldehyde and not more than 10% *w/w* of eugenol.—*S.R.A., F.D., No. 2, Rev. 4, Aug. 1933.*

The aldehyde limits have been restricted in order to eliminate factitious oils containing artificial cinnamic aldehyde and redistilled cassia oil which, although often sold as *B.P.*, lack the true cinnamon oil odour. English distilled oils possess the finest aroma and invariably contain a low percentage of cinnamic aldehyde. Some years ago imported oils frequently contained a large proportion of cinnamon leaf oil but they are no longer marketed.—C. T. Bennett, *Pharm. J.*, 1933, 150.

Analytical characters which differ from the *B.P.* but which are more in conformity with true cinnamon oil are given by Gildermeister and Hoffman, *Die Ätherischen Öle*, as follows:—Sp. gr., 1.023 to 1.040; α_D , 0° to -1° , seldom more; $n_{D20^{\circ}}$, 1.581 to 1.591; aldehydes, 65% to 75%; eugenol, 4% to 10%; soluble in 2 to 3 volumes of 70% alcohol. Oils containing less than 65% or more than 5% of cinnamic aldehyde are suspect.

Genuine oils frequently fail to dissolve 1 in 3 of 70% alcohol, but are usually soluble in 4 to 5 parts.—Finnemore.

For details of *C. zeylanicum* root, bark, and leaf oils, and *C. cassia* oil, see *Bull. imp. Inst., Lond.*, 1921, 19, 323, per *Quart. J. Pharm.*, 1922, 63.

Powdered cinnamon stored in paper bags lost 11% to 33% of essential oil; stored in glass it lost 0% to 8% during one year.—I. Horváth, per *Quart. J. Pharm.*, 1933, 607.

For methods and yields of distillation of cinnamon bark and leaf in the Seychelles, see Haines, *Bull. imp. Inst., Lond.*, 1934, 32, 551. At the present time only cinnamon leaf oil is produced. The distillation of the bark, from which an oil with low aldehyde content (about 36%) was obtained, has now ceased.

COCAINA

Cocaina (*B.P.* '32). $C_{17}H_{21}O_4N=303\cdot2$. M.p., 97° to 98° . Ash, not more than 0·1%. Tests for absence of isoatropyl-cocaine and limit of cinnamyl-cocaine are included. The lower limit for the melting-point in the *B.P.* is too high, the majority of commercial samples having a melting-point of about 96° to 97° .

Constitutionally, cocaine is ecgonine with the hydrogen atoms in the carboxyl and hydroxyl groups replaced by a methyl and benzoyl group respectively.

The physiological activity of cocaine is connected with the presence of the acylated hydroxyl group in the γ position with regard to the nitrogen atom in the ring. Synthetic proof.—*Ann. rep. Chem. Soc.*, 1919 (Vol. XV), p. 110.

Extraction of (crude) cocaine is conducted in the following stages:—

(1) Treatment with sulphuric acid 0·5%; (2) the liquor is rendered alkaline with sodium carbonate, avoiding excess; (3) stirring with petroleum for 3 or 4 hours; (4) extraction of the solvent with acid 0·3%, then this with the required amount of alkali. Collect and wash. The pasty mass contains 87% to 93% of pure cocaine.—O. Sperber, *Tropenpflanzer*, 1911, 15, 684—687, per *J. Soc. chem. Ind., Lond.*, 1912, 44.

Purification of crude cocaine. Cocaine, truxilline and cinnamyl-cocaine being ecgonine derivatives, yield ecgonine, acids, and methyl alcohol on hydrolysis. This fact is of importance commercially as the amorphous residue remaining after extracting as much as possible of the crystalline cocaine can be converted into ecgonine, and this by treatment with benzoic anhydride and methyl alcohol can be converted synthetically into cocaine.

Although formerly care was taken in the extraction to preserve the cocaine, manufacturers now rely on the ecgonine content. After isolation of the crude "cocaine," it is treated so as to reintroduce the methyl and benzoyl groups.

β -Naphthalenesulphonic acid may be used for purifying crude cocaine. Crude cocaine, 10 g., is dissolved in hot water containing 5 g. of the acid and the solution filtered warm. On cooling, an oily resinous body deposits which becomes semi-crystalline. Ammonium carbonate is added, then solution of ammonia which produces a white precipitate. This is extracted with ether and the pure cocaine crystallises out from the ethereal solution. The acid used may be recovered by concentrating the mother liquors and precipitating with hydrochloric acid.

Another method is to dissolve crude cocaine in boiling water containing acetic acid. On cooling, precipitate with ammonium carbonate yielding a resinous yellow precipitate lighter than water. The solution is filtered and ammonia added. The cocaine is crystallised from ether.

The ecgonine contained in the resinous precipitate can be worked up. The residue is purified by crystallisation from alcohol and pure ecgonine precipitated by sodium carbonate. It is dissolved in methyl alcohol and the solution treated with anhydrous hydrochloric acid. Of the methylecgonine obtained, 20 g. is heated on a water-bath with benzoyl chloride, 20 g., until no more hydrochloric acid is evolved. The solution is added to cold water. Benzoic acid is precipitated. This is filtered out and the filtrate concentrated. The synthetic cocaine (termed coca-ethyline in the German Patent 47,713) is then precipitated from the filtrate by means of ammonia.—De Rosemont, *J. suisse Pharm.*, Apl. 29, 1920, per *Chem. & Drug.*, ii/1920, 934.

Tests for Cocaine

PERMANGANATE TEST. When a drop of a solution of cocaine is placed on a dried film formed by a solution of potassium permanganate on a micro slide and examined under the microscope, oily drops are seen. If, however, the cocaine is dissolved in a saturated solution of alum, violet crystals of cocaine permanganate will quickly be observed. Alypin, tropacocaine and scopolamine produce crystals from aqueous solutions. Beta-eucaine, stovaine, novocain and holocain form no crystals with permanganate. Saporetti's bromine test distinguishes.—*Pharm. J.*, i/1911, 94.

REICHARD'S TEST consists in adding a concentrated solution of sodium nitroprusside, drop by drop, to a cocaine salt solution containing at least 0·004 g. cocaine per millilitre. A precipitate of reddish crystals is formed which dissolves on warming and reappears after the liquid is cooled.

PISANI'S TEST. A wine-red colour is obtained by heating together cocaine or cocaine hydrochloride with a few drops of concentrated sulphuric acid containing 2% formamide. The colour soon disappears, giving place to a brownish-grey precipitate. The test is stated to detect 0.001 g. cocaine.—Autenreith, *Detection of Poisons and Powerful Drugs*.

With chromic acid and cobalt nitrate, alypin behaves similarly to cocaine and eucaïne and precipitates with usual alkaloidal reagents, caustic and carbonated fixed alkalis, and ammonia.

The four alkaloids, cocaine, truxilline, $C_{19}H_{23}NO_4$ (also called cocamine or isoatropyl-cocaine), cinnamyl-cocaine and tropacocaine, $C_8H_{14}NO, C_8H_5CO$, are known to exist in coca leaves.

VITALI'S REACTION. Cocaine gives a reaction similar to atropine if the alkaloidal residue, after mixing with alcoholic solution of potassium hydroxide, is heated on the water-bath, but gives no reaction in the cold—the reaction in this case, however, is found to be due to isoatropyl-cocaine as impurity.—*Yearb. Pharm.*, 1922, 7. Further experiments to show that the colour is due to esters of the tropic acid series.—*Yearb. Pharm.*, 1923, 24.

Cocainæ Hydrochloridum (*B.P.* '32). $C_{17}H_{21}O_4N, HCl = 339.6$. M.p. not lower than 197° , when placed in the heating bath at 193° . Specific rotation in 2% *w/v* aqueous solution, -70° to -72° . Ash limit, 0.1%.

It should not only be in good crystals, but should, by the following modification of MacLagan's Test, yield a distinctly crystalline precipitate of pure cocaine within 3 minutes when 1 grain is dissolved in 2 oz. of distilled water, and 6 to 8 drops of dilute solution of ammonia, *B.P.*, are added and well stirred. If more than 4% of amorphous alkaloid (principally truxilline) be present, there will be only a cloudiness. The precipitate redissolves after 24 hours or more, the cocaine being converted into methyl alcohol and benzoylecgonine. Truxilline is highly toxic. (Fr. Cx. also gives this test and states the same. *P.G. VI* gives it in a modified form.)

Sterilisation of Cocaine Hydrochloride Solutions. Deterioration has been reported not only in anæsthetic power but also in vasoconstrictor effect (see *Pharm. J.*, ii/1934, 501).

Definite evidence, at any rate with 2% solution in ophthalmic work (see *Edn. XVIII*, Vol. II, p. 63), shows that boiling is safe.

Efficiency of cocaine solutions is not impaired by boiling.—Rep. Com. Local Anæsthetics.—*Chem. Abstr.*, 1922.

Cocæ Folia. The leaves from BOLIVIA, PERU and CEYLON contain cocaine as their chief alkaloid, whilst the JAVA leaf contains chiefly cinnamyl-cocaine, but little or no cocaine, chemical treatment being necessary to convert the alkaloids into cocaine. The genus *Erythroxylon*, which yields cocaine alkaloids and is indigenous to 4 continents, comprises about 80 species of which only 4 or 5 have so far been completely examined as regards alkaloidal content. The commercial supply comes from at least three distinct species. Suggested control of cocaine traffic by restricted production of coca leaves may prove more difficult than expected.—*Plant Alkaloids*, T. A. Henry, reviewed, *Brit. med. J.*, ii/1924, 626.

Folium Cocæ, *P. Helv. V*, is the dried leaf of *Erythroxylon Coca* Lamarck, and contains not less than 0.7% of alkaloid.

Liquid Extract of Coca. The *B.P.C.* assay requires modification. The extraction of the alkaloids from ammoniacal solution should be made with successive portions of ether until complete, and sufficient dilute acid should be used to extract the alkaloids completely. The final ethereal solution must be washed with a little water to remove any traces of ammonium salts and the final residue dehydrated with absolute alcohol and heated at 80° for 2 hours to remove volatile bases.—W. A. Markwell, *Pharm. J.*, i/1935, 416.

COCAINE SUBSTITUTES

Amydricainæ Hydrochloridum (*B.P.C.* '34). $C_{16}H_{26}O_2N_2, HCl = 314.7$. M.p., about 169° . Loss at 100° , not more than 2%. Ash, not more than 0.1%.

Amylocainæ Hydrochloridum (*B.P.* '32). $C_{14}H_{21}O_2N, HCl = 271.6$. M.p. 177° to 179° . Ash, not more than 0.1%.

Benzaminæ Hydrochloridum (*B.P.C.* '34). $C_{15}H_{21}O_2N, HCl = 283.6$. M.p., about 268° , with decomposition. Loss at 100° , not more than 1%. Ash, not more than 0.1%.

Benzaminæ Lactas (*B.P.C.* '34). $C_{15}H_{21}O_2N, C_3H_6O_3 = 337.2$. M.p., 152° to 156° . Loss at 100° , not more than 1%. Ash, not more than 0.1%.

Benzocaina (*B.P.* '32). $C_9H_{11}O_2N=165.1$. M.p., 90° to 91° . Ash, not more than 0.1%.

Orthocaina (*B.P.* '32). $C_8H_9O_3N=167.1$. M.p., 141° to 143° . Loses not more than 1% at 100° . Ash, not more than 0.1%.

Procainæ Hydrochloridum (*B.P.* '32). $C_{13}H_{20}O_2N_2.HCl=272.6$. M.p. 154° to 156° . Ash limit, 0.1%. The *U.S.P.* X substance leaves a negligible ash. Procainum, m.p. 60° to 62° , Procainum hydrochloricum, m.p. 153° to 154° , and Procainum nitricum, m.p. 100° to 102° , are official in the *P. Helv. V.*

Quantitative methods for the determination of procaine hydrochloride are described in *Methods of Analysis (A.O.A.C., 1930, 471)*.

Solutions of novocain may be sterilised in slightly alkaline glass vessels at 100° without change, but at 120° the alkali causes appreciable change.—*J. chem. Soc. Abstr.*, ii/1925, 247.

For tests for identification see *Scheme for Recognition of Organic Substances*.

Pharmacology of Local Anæsthetics (Cocaine and substitutes) Eggleston and Hatcher, (*J. Pharmacol.*, Vol. XIII, 1919) found that "five, or more than five, times the minimal fatal vein dose of alypin, beta-eucaine, stovaine and tropacocaine can be injected subcutaneously in the cat without causing death while four, or less than four, times the fatal vein doses of cocaine and holocain similarly injected prove fatal"; further, that "the simultaneous subcutaneous injection of adrenalin with the local anæsthetics reduces the toxicity of the latter by delaying absorption rate, but this reduction is much less marked in the cases of cocaine and holocaine than with the other members of the series, and is referable to their much slower 'essential' elimination."

A committee appointed by the American Medical Association to study the occurrence of accidents arising from the use of local anæsthetics reported 4 hitherto unpublished deaths, of which cocaine was responsible for 23. Novocain was found to be the most frequently employed and by far the safest. Butyn, cocaine, alypin, apothesine and stovaine are probably equally dangerous when injected into the tissues. The committee advised that cocaine should not be given hypodermically, neither should concentrated solutions be applied to the mucous membranes. Not more than 15 minims of 10% cocaine should be applied to the throat or nose and not more than 1.5 grains given when applied to the mucous membrane—urethral injections especially dangerous. Novocain should not be injected in concentrations above 1%, and butyn should not be injected but may be applied in 2% solution.—*Brit. med. J.*, i/1924, 871.

COLCHICUM

Colchici Cormus (*B.P.* '32). Contains not more than 2% of other organic matter. The corm dried at 65° contains not less than 0.25% of colchicine. Assayed by the same process as the seed, but subtracting the amount of the final residue which is insoluble in cold water. Colchici Cormus, *U.S.P. X*, should yield not less than 0.35% of colchicine.

The fresh corm is not used in the *B.P.* and the inclusion of a standard serves no useful purpose.—*Pharm. J.*, ii/1932, 87.

Assay of colchicum by phosphotungstic acid.—E. C. Davies, *Pharm. J.*, i/1921, 505. Iodine may also be employed as precipitant.

Estimation by shaking out the alkaloid with chloroform and precipitating with phosphotungstic acid (Scheibler's reagent). Precautions necessary in estimating colchicine due to the presence of an amino-acid grouping.—J. Griebl, *Pharm. J.*, ii/1923, 87.

For the methods upon which the *B.P.* processes were formulated see P. A. V. Self and C. E. Corfield, *Quart. J. Pharm.*, 1932, 347.

Colchici Semen (*B.P.* '32). Other organic matter, not more than 2%. Contains not less than 0.3% of colchicine. Ash limit, 3%. Assayed by continuous extraction with alcohol, filtering the cooled and settled liquid, and evaporating to dryness; the solution of the residue in 20% *w/v* sodium sulphate

lution is cleaned with ether, cleared with talc and filtered; an aliquot part of the filtrate is again cleaned with ether, shaken with chloroform, N/1 sodium hydroxide added and the alkaloid completely extracted with chloroform; the chloroform is evaporated, two portions of alcohol added and evaporated, and the residue dried at 100° and weighed. Colchici Semen, *U.S.P. X*, yields not less than 0.45% of colchicine, when extracted by a lead subacetate process, the weight of residue insoluble in N/20 sulphuric acid with chloroform being deducted from the weight of residue from chloroform extraction. Semen Colchici, *P. Helv. V*, contains not less than 0.5% of colchicine and the powder for administration is adjusted with lactose to contain 0.4% of colchicine.

Colchicina (*B.P.C. '34*). Ash, not more than 0.1%. Tests for limit of chloroform compound and of colchicine are described. Colchicinum, *P.G. VI*, $C_{22}H_{25}O_6N, \frac{1}{2}CHCl_3$, contains 87% of colchicine. Colchicinum, *P. Helv. V*, is the crystalline alkaloid, $C_{22}H_{25}O_6N + 1\frac{1}{2}H_2O$, containing from 6% to 7% of water of crystallisation.

COLOCYNTHIS

Colocynthis (*B.P. '32*). Should contain not more than 5% of seeds, 2% of outer sclerenchymatous pericarp, and should yield not more than 8% of acid-insoluble ash, and not more than 3% of light petroleum extractive dried at 100°. The *U.S.P. X* limit of petroleum ether extractive is 2% dried at 110°, and of acid-insoluble ash, 6%.

COLOPHONIUM

Colophonium (*B.P. '32*). Acid value, 150 to 180. Ash, not more than 0.1%. Resina, *U.S.P. X*, should have a sp. gr. at 25° of 1.07 to 1.09, an acid number not less than 150, and should leave not more than 0.05% of ash.

Guaiaci Resina (*B.P.C. '34*). Should leave not more than 10% of matter insoluble in alcohol and not more than 4% of ash; should comply with a test for absence of colophony. Guaiacum, *U.S.P. X*, has a m.p. of 85° to 90° and gives no reaction for rosin with copper acetate.

CORIANDRUM

Coriandrum (*B.P. '32*). Limits: for foreign organic matter, 2%; for ash, 7%; and for acid-insoluble ash, 1%. Coriandrum, *N.F. V*, should contain not more than 5% of other fruits, seeds or foreign organic matter, and should yield not more than 1.5% of acid-insoluble ash; ether-soluble extractive, not less than 0.5%.

The Food and Drug Administration of the U.S. Department of Agriculture define coriander seed as the dried fruit of *Coriandrum sativum* L. Contains not more than 7% total ash, and not more than 1.5% of ash insoluble in hydrochloric acid.—*S.R.A., F.D., No. 2, Rev. 4, Aug., 1933.*

Oleum Coriandri (*B.P. '32*). Sp. gr. 0.870 to 0.884. α_D , +8° to +15°. n_{D20}° 1.462 to 1.472. Should be soluble in 3 volumes of alcohol (70%, sp. gr. 0.8896 to 0.8901). The *U.S.P. X* requires the oil to comply with the same solubility test; sp. gr. at 25°, 0.863 to 0.875; α_D , +8° to +13° at 25°. n_{D20}° 1.4630 to 1.4760.

CRESOL

Cresol (*B.P.* '32). Sp. gr., 1·035 to 1·050. Distillation range, not more than 2% *v/v* below 188° and not less than 80% *v/v* between 195° and 205°. Not less than 90% *v/v* of cresol, *U.S.P. X*, should distil between 195° and 205°. Cresolum crudum, *P.G. VI*, contains not less than 50% of *m*-cresol when determined by nitration and weighing the trinitro-*m*-cresols produced. Cresolum crudum, *P. Helv. V*, must contain at least 50% of *m*-cresol.

The new *B.P.* specification permits much greater variation than that of the *B.P.* '14. One cresol may consist of isomeric cresols while another may contain 20% of higher homologues.—*Pharm. J.*, ii/1932, 87.

British Standard Specifications:—

B.S.S. No. 522—1933, includes specifications for: (1) Orthocresol (522A), crystals or masses having a crystallising-point of 30·3° to 31·0° and a boiling-point of about 191°; (2) Metacresol (522B), colourless to very pale straw-coloured liquid or solid of sp. gr. 1·037 to 1·040 and having a crystallising-point of not below 10·5° and a boiling-point of about 202°; (3) Paracresol (522C), crystals or masses having a crystallising-point not lower than 34° and a boiling-point of about 202°.

B.S.S. No. 517—1933, describes Cresylic Acid of high orthocresol content. It must contain not less than 45% of orthocresol; the sp. gr. is from 1·045 to 1·050 at 15·5°, and 90% distils between 192° and 200°. The proportion of orthocresol is determined by observing the crystallising-point of a mixture of the sample and pure cineole under carefully controlled conditions.

B.S.S. No. 521—1933, describes the variety of commercial cresol known as Cresylic Acid (50/55% Metacresol), a liquid having a specific gravity of 1·035 to 1·040 at 15·5° and of which approximately 92% distils between 199° and 204°. The proportion of metacresol is determined by a nitration process and weighing the washed solid trinitrometacresol produced.

B.S.S. No. 524—1933, includes specifications for Refined Cresylic Acids. Refined Cresylic Acid, Grade A, is controlled for colour, water content, specific gravity (1·035 to 1·050), distillation (not more than 5% below 192° and at least 90% below 205°), neutral oils and pyridine bases, sulphuretted hydrogen, and freedom from acids and alkalis. Refined Cresylic Acid, Grade B, may contain twice as much water (1%), 10 times as much neutral oils and pyridine bases (1% of each), and at least 80% must distil below 205°.

Tests to distinguish Carbolic Acid, Cresols and other Phenols.

TEST I. Dissolve 1 drop (0·05 g.) of the phenol in 10 ml. of strong hydrochloric acid in a mortar and add 0·5 g. of a mixture of NaNO₃ (1 part), NaNO₂ (1 part) and exsiccated Na₂SO₄ (2 parts). Stir well and allow to stand for 2 to 5 minutes. Note colour and pour 1 ml. of the acid mixture into excess of 10% aqueous NH₄OH and note change of colour.

Carbolic Acid gives a rich crimson colour in 2 minutes. On pouring the mixture into NH₄OH a deep emerald green results. If at the crimson stage 1 or 2 drops of 38% formaldehyde solution are added and the mixture stirred, the colour changes to rich purple and if now poured into NH₄OH a deep blue colour occurs. *Ortho-Cresol*. A dichroic solution is given in the acid, green being predominant. If a drop or two of formaldehyde solution is then added the green changes to blue (purple by transmitted light). If now poured into NH₄OH, only olive-green results. *Meta-Cresol*, *Para-Cresol* and *Cresol* give no distinctive results and are thus easily distinguished from carbolic acid and ortho-cresol. The presence of *p*-cresol also inhibits the reaction with carbolic acid or *o*-cresol, and the test cannot be used for detection of either of these in cresol, *B.P.* *Beta-Naphthol* and *Alpha-Naphthol* give crimson-purple and violet-purple respectively after standing 3 to 5 minutes in the acid mixture. The colours are destroyed by ammonia solution. The acid solution withstands heat and subsequent dilution with retention of colour better than with other phenols. *Thymol*, after stirring and leaving for 5 minutes, gives a pronounced green, becoming yellow on pouring into ammonia solution.

TEST II. Dissolve 1 drop of the phenol in 5 ml. to 10 ml. of strong HCl with a minute crystal (size of pin's head) of NaNO₂. Slowly heat the mixture nearly to boiling; cool or dilute and pour into excess of dilute NH₄OH solution. Note the colour changes.

Carbolic Acid, ortho-cresol and meta-cresol: On pouring the acid solution into NH_4OH and warming, a deep blue colour results. *Para-cresol* gives no colour. In aqueous solution, acidified with acetic acid, together with a little NaNO_2 , and a few drops 1 to 2% CuSO_4 solution, a rich wine-red solution is given, turning to pink on dilution with water. *Guaiacol* gives a green with NH_4OH . *Resorcinol* gives successively brown, red, purple, violet and blue; on diluting with water, green, and on pouring the acid mixture into ammonia solution, a dichroic solution with brilliant red fluorescence, wine-purple to transmitted light. *Orcinol*, *phloroglucinol* and the *catechins* give rather poor reds or purples both before and after treatment with ammonia. *Catchecol* gives a distinct bluish-green in the acid mixture, and *pyrogallol* a purplish colour if heated with a nitrate in the acid mixture.—A. H. Ware, *Analyst*, 1927, 335.

The determination of meta- and ortho-cresols in mixtures of cresols can be made by formation of the aldehyde resins; the amount of ortho-compound can be found by the cineole freezing-point method and, by subtraction, the proportion of meta-cresol can be ascertained.—C. E. Sage and H. R. Fleck, *Analyst*, 1932, 567.

Liquor Cresolis Saponatus (B.P. '32). Should contain 47% to 53% *v/v* of cresol. Assayed by acidifying, extracting with ether, evaporating the ether, and steam distilling the residual liquid at 170° ; the distillate is saturated with salt, extracted with ether, warmed to 170° and the residue weighed, the cresol distilled and the weight of water, etc., and non-volatile residue subtracted; the distilled cresol should have the sp. gr. and b.p. of cresol. **Liquor Cresolis Compositus**, U.S.P. X, is assayed by distillation with kerosene and extraction of the distillate with sodium hydroxide, when the proportion of cresol, measured by the increase in volume of the sodium hydroxide solution used, should be from 46% to 52% *v/v*; the cresol separated from this solution should comply with the distillation standard for cresol. **Liquor Cresoli saponatus**, P.G. VI, contains about 50% of crude cresol and 25% of fatty acids from linseed oil.

Assay of Cresols in Lysol. The following method is more suitable and accurate than that of the B.P. when only normal quantities of lysol are available. It can be used for less concentrated preparations of cresols and the higher homologues of phenol and for other coal tar disinfectants in which the phenols are dissolved in, or emulsified with, solutions of soaps or resins.

Weigh 25 to 100 g. of the liquid, according to the amount available and the phenolic content of the preparation, into a conical flask and shake with 100 ml. of water; add 15 to 50 g. of solid barium hydroxide and heat for one hour under a reflux condenser by immersing the flask in boiling water, shaking well at frequent intervals. After cooling, pour off the aqueous liquid and filter, washing the residue, and finally the filter, with hot barium hydroxide solution. Acidify the filtrate in a separating funnel with hydrochloric acid, saturate the mixture with calcium chloride and extract the liberated phenols with successive small portions of ether. Transfer the ethereal solutions to a small flask, evaporate off the ether, dry the phenolic residue to constant weight by heating on a water-bath and finally over sulphuric acid. The weight obtained gives the quantity of crude phenols in the weight taken, and the percentage by volume may be calculated from the specific gravity of the crude phenols obtained and that of the original liquid. The nature of the phenols recovered may be ascertained by submitting the residue to fractional distillation and weighing separately portions of the distillate collected within the boiling-ranges of phenol, cresols and the higher homologues.

The following are references to other methods:—

100 g. of lysol treated with excess 2% sulphuric acid, and the fatty acids and cresols extracted with 50 and 20 ml. of ether. The ethereal layer is dried over sodium sulphate and distilled, and the phenols collected between 180° and 230° .—A. H. Dodd, *J. Soc. chem. Ind., Lond.*, 1924, 931.

Cresols in lysols approximately estimated by steam distillation of 60 g. to 70 g. after acidifying with 30 ml. to 35 ml. of dilute sulphuric acid. The weight of cresol in the sample is obtained by multiplying the volume of cresols in the distillate by 1.04 and adding $1/50$ of the volume of the aqueous layer. Method gives trustworthy results.—C. J. Jordan and F. Southerden, *Analyst*, 1921, 375.

Data given of a large number of examinations of castor oil and linseed oil lysols.—*Pharm. J.*, i/1921, 479.

Accurate results by distillation can only be assured when the soap is known to be free from volatile fatty acids. It is best to dissolve the sample in hot water in a separator, add a piece of stick caustic soda and shake until dissolved. Add excess of brine and separate. Redissolve in hot water, add caustic soda and again salt out; repeat again. Acidify the united alkaline liquors and extract with benzene. Extract this solution with a small quantity of caustic soda, acidify and read off in the usual way.—G. F. W. Martin, *Yearb. Pharm.*, 1922, 142.

Present-day lysols vary appreciably in characters and properties but very little adjustment will be necessary to make them comply with the official strength. The assay process is unnecessarily complicated and there is confusion between crude cresol and separated cresol. A large proportion of the higher phenols (non-volatile residue) is lost and it is useless to examine the separated cresol to see that it comes within the *B.P.* boiling-range.—*Pharm. J.*, ii/1932, 107.

The lysol supplied by the large manufacturers would comply with a requirement of miscibility with water up to 10%, or even 20%, of lysol, but does not in the majority of cases, comply with the requirement of miscibility in all proportions. The statement of miscibility with ether does not hold for commercial samples.—G. R. Page, *Quart. J. Pharm.*, 1934, 369.

Creosotum (*B.P.* '32). Sp. gr., not less than 1.070. Distillation commences at about 200°, and not less than 95% *v/v* is collected between 200° and 230°. **Creosotum**, *U.S.P. X*, has a sp. gr. of 1.076 at 25°. Not less than 90% *v/v* should distil between 200° and 220°.

Genuine beechwood creosote yielded 39% of monophenols, 26.48% of guaiacol, and 32.14% of creosol, $C_6H_3 \cdot CH_3 \cdot OCH_3 \cdot OH$, and homologues. **Pinewood creosote** about the same but 20.3% guaiacol and 37.5% of creosol and homologues—all boiling between 200° and 210°.

Creosote is usually optically inactive but may be slightly dextrorotatory.

Creosoti Carbonas (*B.P.C.* '34). Sp. gr., 1.150 to 1.180. Ash, not more than 0.1%. Free creosote is excluded by the absence of any green colour developing on addition of ferric chloride to the alcoholic solution. The *U.S.P. X* specifies a sp. gr. at 25° of not below 1.145; 85% of the separated creosote should distil between 200° and 220°, which should not respond to the tests for hydrocarbons and coal-tar creosote for **Creosotum**, *U.S.P. X*.

Guaiacol (*B.P.* '32). The liquid form has a sp. gr. of 1.116 to 1.125, and the crystals a m.p. of about 28°. Between 200° and 210°, not less than 95% should distil. **Guaiacol**, *U.S.P. X*, should have a sp. gr. at 25° of not below 1.112 for the liquid and of about 1.132 for the melted solid; the solid boils between 204° and 206° and not less than 85% of the liquid distils between 200° and 210°.

Guaiacolis Carbonas (*B.P.C.* '34). $C_{15}H_{14}O_5 = 274.1$. M.p., 85° to 88°. Ash, not more than 0.1%. Should comply with a test for absence of free guaiacol. The *U.S.P. X* substance should leave not more than 0.1% of ash.

Potassii Guaiacolsulphonas (*B.P.C.* '34). $C_7H_7O_5SK = 242.2$. Should give not less than 35.2% of sulphated ash, corresponding to not less than 98% of the pure substance. The composition is stated to be represented by the formula $C_6H_3(OCH_3)(OH)SO_3K(1 : 2 : 3)$.

Kalium sulfoguaiacolicum, *P.G. VI*, contains not less than 96.9% of $C_6H_3(OH)(OCH_3)SO_3K(1 : 2 : 4 \text{ and } 1 : 2 : 5)$. **Kalium guaiacol sulfonicum**, *P. Helv. V*, is described as a mixture of salts of 1-oxy-2-methoxybenzene-4-(and 5)-sulphonic acids and is required to give from 35% to 39% of sulphated ash.

The potassium salts of guaiacolsulphonic acid may be determined by titration with N/10 sodium hydroxide to Poirrier-blue, followed by titration with N/10 hydrochloric acid using alizarin-yellow R as indicator.—*Brit. chem. Abstr. (B)*, 1933, 171.

CROCUS

Crocus (*B.P.C.* '34). Should lose not more than 12.5% of moisture and then yield not less than 60% of alcohol (60% extractive; styles and anthers, not more than 8%, and foreign organic matter, not more than 2%; ash, not more than 7.5%; light petroleum extractive, not more than 1%. The *N.F. V*

allows not more than 10% of yellow styles, not more than 2% of foreign organic matter and not more than 7.5% of total ash.

The Food and Drug Administration of the U.S. Dept. of Agriculture define saffron as the dried stigma of *Crocus sativus* L.; contains not more than 10% of yellow styles and other foreign matter, not more than 14% of volatile matter when dried at 100°, not more than 7.5% of total ash, and not more than 1% of ash insoluble in hydrochloric acid.—*S.R.A., F.D., No. 2, Rev., 4, Aug. 1933.*

Adulteration of saffron with carthamus flowers and calendula can be detected by the orange-red or clear-blue fluorescence of the material when exposed to ultra-violet light.—A. Castiglione, *Ann. Falsif.*, 1933, 26, 41.

CUPRUM

B.P. Limit Test for Copper. The copper limit tests of the *B.P.* may be replaced by a colorimetric method using sodium diethyldithiocarbamate. A standard copper solution containing 0.00001 g. of Cu per ml. (or 0.0393 g. of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ per litre) is prepared by diluting 5.67 ml. of standard Fehling's copper sulphate solution to 100 ml. and diluting 10 ml. of the resulting solution to 1 litre. The reagent is used as a 0.1% aqueous solution. The copper content is determined by adding 1 ml. of dilute ammonium hydroxide solution and 10 ml. of the reagent to the test solution contained in a 100 ml. Nessler glass and comparing the colour produced with that obtained by treating similarly aqueous dilutions of known volumes of the standard copper solution. The method is inapplicable to bismuth compounds. For iron salts the iron must be removed by oxidation to the ferric state and precipitation with ammonium hydroxide, the copper being determined in the filtrate. Lead salts may be removed by adding a ferric salt and precipitating both with ammonium hydroxide. It is not necessary to extract the coloured compound with a solvent.—F. J. Flowerdew, *Pharm. J.*, i/1934, 413.

The coloured compound should be extracted with carbon tetrachloride before comparing the colours. The precipitation of ferric hydroxide causes a serious loss of copper and the diethylthiocarbamate reagent is too sensitive for medicinal substances.—N. Evers and L. A. Haddock, *Pharm. J.*, i/1934, 452.

Minute amounts of Cu are found in chemicals and galenicals. In view of the value of such traces in hæmoglobin formation it is unlikely that they would be harmful.—N. Evers and L. Haddock, *Quart. J. Pharm.*, 1932, 458.

Copper in various chemicals ranged from 0.4 parts per million in hydrochloric acid to 68 in ferric glycerophosphate, and in galenicals from 4 in ammoniated tincture of valerian to 580 in *B.P.* 1914 extract of ergot.—N. Evers and L. A. Haddock, *Quart. J. Pharm.*, 1932, 458.

To Kill Algæ in Ponds, etc. It is stated that, without injury to plants or fish, copper sulphate not exceeding $2\frac{1}{2}$ oz. per 10,000 gal. may be employed. The crystals should be slightly crushed, placed in a coarse bag and drawn to and fro across the pond. To estimate the amount of water in the pond multiply together the average length, breadth and depth expressed in feet. This result multiplied by $6\frac{1}{4}$ will give the number of gallons. If the first application does not suffice, repeat in a week or ten days.

Organic Copper Compounds.

Cupri Alloxanas. $(\text{N}_2\text{C}_4\text{O}_4\text{H})_2\text{Cu}$. A bluish-green flocculent powder slightly soluble in water. The relative insolubility is a disadvantage from the therapeutic standpoint.

Cupri Glycinas. $(\text{NH}_2\text{CH}_2\text{COO})_2\text{Cu}$. A blue flocculent silky powder soluble about 1 in 200 of water at 15°, but more than twice as soluble at 40°. 0.06 g. per kilo in 0.5% solution intravenously killed a rabbit in 8 minutes, whilst a control of salvarsan in proportion 0.1 g. per kilo was tolerated, hence the substance has a toxic dose of about 2 g. for an average man.

Cupri Hippuras. $(\text{C}_6\text{H}_5\text{CO} \cdot \text{NHCH}_2\text{COO})_2\text{Cu}$. A bluish-green crystalline powder. Almost insoluble in water, but soluble about 1 in 200 of a mixture of glycerin and water equal parts. It is more soluble in pure glycerin.

Rats maintained for 2 or 3 months on diets containing a high proportion of peas to which copper was added grew normally and did not suffer in health. Most of the copper is excreted by the alimentary tract; a small proportion may be absorbed in the blood, retained in part for a time by the liver and then excreted by the kidneys.—*Brit. med. J.*, i/1924, 680.

DERRIS

Derris (*B.P.C.* '34). By continuous extraction with carbon tetrachloride, concentrating, and standing at 0° (seeding if necessary), filtering and air-drying not above 40°, crystals of the carbon tetrachloride compound equivalent to not less than 2% of rotenone are obtained; (factor 0.719). Ash, not more than 6%; acid insoluble ash, not more than 2%.

Commercial samples examined by the carbon tetrachloride process have been shown to contain from nil to 6.9% of rotenone.—*Bull. imp. Inst., Lond.* 1933, 32, 469.

The carbon tetrachloride method of determining rotenone gives results which are low if the rotenone content of the resin (either isolated or present in the root) is below about 17%, and is seriously in error if the rotenone content of the resin is below 10%. It fails completely for resins of very low rotenone content. A resin may contain up to 15% of rotenone, i.e., 2.4% of rotenone in the root, and yet give no rotenone by the standard method of determination. The rotenone-carbon tetrachloride crystals which separate in the determination of rotenone are at most 90% to 95%, probably only 80% to 90%, pure.—R. S. Cahn and J. J. Boam, *J. Soc. chem. Ind., Lond.*, 1935, 37T.

Constituents. In addition to rotenone, a dimorphic substance (m.p. 189 and 192° to 194°), isomeric with tephrosin, $C_{23}H_{22}O_7$, and having insecticidal properties, has been isolated from derris. Published data on the relative toxicities of rotenone, deguelin, tephrosin, and toxicarol are inapplicable to the assessment of the toxicity of derris resin, as the last three compounds do not occur as such (or, at most, in very small amounts) in derris resins. The conclusion, often drawn from published data, that the value of a derris root or resin can only be assessed by its rotenone content, is quite unjustified.—*ibid.* 42T.

Rotenone

Colour Test. To 1 ml. of solution in acetone add 1 ml. of diluted nitric acid (1 part acid and 2 parts water) and allow to stand for 30 seconds. Dilute with 8 or 9 ml. of water and add 1 ml. of strong solution of ammonia. A blue colour is produced with 0.0001 g. of rotenone.—H. A. Jones and C. M. Smith, *Industrial Engng Chem., Anal. Edn.*, 5, 1, 75.

The purity of commercial rotenone can be determined colorimetrically by means of the red colour produced when nitric acid and sodium nitrite are added to a mixture of a solution of the sample in acetone and an equal volume of 10% solution of potassium hydroxide in 95% alcohol. Standard conditions must be employed.—C. R. Cross and C. M. Smith, *J. Ass. off. agric. Chem. Wash.*, 1934, 17, 336.

Tuba or derris is a well-known Malay fish poison; the root is bruised in water with lime and the milky emulsion thrown into the stream.

A dessertspoonful placed in the entrance hole will destroy a wasp's nest.—*Pharm. J.*, ii/1933, 194.

DEXTROSUM

Dextrosum (*B.P.* '32). $C_6H_{12}O_6 = 180.1$. Loses not more than 2.5% at 105°, and then a well-boiled 10% *w/v* solution has specific rotation of not less than +52°. Residue after ignition on re-ignition with sulphuric acid, not more than 0.1%. The *U.S.P. X* allows a moisture limit of 10% at 105°. *Glycosum P. Helv. V*, is pure anhydrous dextrose containing not more than 1% of moisture.

The Food and Drug Administration of the U.S. Dept. of Agriculture defines dextrose as the product chiefly made by the hydrolysis of starch or a starch-containing substance, followed by processes of refining and crystallisation.

Anhydrous dextrose contains not less than 99·5% of dextrose and not more than 0·5% of moisture. *Hydrated dextrose* contains not less than 90% of dextrose and not more than 10% of moisture including water of crystallisation. *Glucose* is a thick, syrupy, colourless product made by incompletely hydrolysing starch, or a starch-containing substance, and decolorising and evaporating the product. It contains, on a basis of 41° Baumé, not more than 1% of ash, chiefly chlorides and sulphates.—*S.R.A., F.D., No. 2, Rev. 4., Aug. 1933.*

Reducing sugars may be determined quantitatively by titration of boiling alkaline solution with potassium ferricyanide containing methylene blue as indicator. The method has also been used for sucrose, lactose in milk, glucose in urine and mixtures of maltose and glucose.—*S. W. Cole, Biochem. J., 1933, 723.*

Glucosum Liquidum (*B.P. '32*). n_{D20° , not less than 1·490. Ash, not more than 0·6%. Sulphur dioxide limit, 450 parts per million. By evaporation with water and drying at 90°, *Glucosum, U.S.P. X*, loses not more than 21% of its weight; ash, not more than 0·5%.

Lactosum (*B.P. '32*). $C_{12}H_{22}O_{11}, H_2O = 360\cdot2$. A 10% *w/v* boiled solution has a specific rotation, determined at 20°, of +52° to +52·6°. Ash, not more than 0·1%. Tests for more soluble sugars, copper and acidity are included. *Lactosum, U.S.P. X*, should leave not more than 0·1% of ash, and should comply with tests for dextrin, sucrose or glucose, and starch.

The *B.P.* limit for more soluble sugars is too low and might well be trebled.—*G. J. W. Ferrey, Quart. J. Pharm., 1933, 411.*

Samples of British and New Zealand lactose generally contain about 0·006 to 0·008 g. per 5 g.

Lævulosum (*B.P. '32*). $C_6H_{12}O_6 = 180\cdot1$. Determined at 20° on a well-boiled 10% *w/v* aqueous solution, the specific rotation should be not less than -81°. Loss at 105°, not more than 5%. Sulphated ash, not more than 2·5%.

Mel Depuratum (*B.P. '32*). Sp. gr., 1·359 to 1·361. α_D for a 20% *w/v* decolorised solution, +0·6° to -2°, corresponding to a specific rotation of +3° to -10°. Ash, not more than 0·3% *w/w*. Artificial invert sugar is excluded by adding one drop of resorcinol in hydrochloric acid solution to an evaporated theareal extract, when no persistent cherry-red or brown-red colour should be produced. *Mel, U.S.P. X*, should comply with tests for acidity, starch or dextrans, foreign colouring matter, azo dyes, and with the following test for artificial honey or added invert sugar:—

If 1 g. of honey be triturated with 20 ml. of ether in a mortar, filtered, the filtrate allowed to evaporate, and 1 drop of a 1% resorcin solution in hydrochloric acid added, a pink colour may form which disappears in half a minute, but an orange, cherry or brown-red colour must not be produced.

Sucrosus (*B.P. '32*). $C_{12}H_{22}O_{11} = 342\cdot2$. Specific rotation in 10% *w/v* solution, +66° to +66·7°. Ash, not more than 0·05%. The absence of ultramarine should be indicated by the absence of unpleasant odour in one hour on the addition of dilute hypophosphorous acid to the clear, colourless, odourless solution. The *U.S.P. X* determines the specific rotation on a 26% *w/v* solution of *Sucrosus* dried at 105°, and in a 200 mm. tube; it should not be less than +65·9°.

Sucrose may (in the absence of a polarimeter) be approximately estimated by heating 1 g. in 50 ml. of water, to which 10 drops of hydrochloric acid have been added, for half an hour on a water-bath. The solution is then boiled and neutralised with soda and made up to 100 ml. with water, and the invert sugar thus formed is estimated with Fehling's solution, 1 ml. of which is approximately equivalent to 0·005 g. of invert sugar, the calculation being on the basis that 360 of invert sugar represents 342 of cane sugar.

Determination of Invert Sugar in Cane Sugar. *U.S.P. X* gives the following: Dissolve 20 g. sucrose in enough distilled water to make 100 ml.; filter if necessary. To 50 ml. of the clear liquid add 50 ml. of alkaline cupric tartrate solution: heat the mixture so that 4 minutes are required to bring it to boiling point and boil for 2 minutes. Add 100 ml. of cold recently boiled distilled water, and collect and weigh the precipitated cuprous oxide as follows. Prepare a Gooch crucible with an asbestos layer. Wash the asbestos with distilled water, followed successively by 10 ml. of alcohol and 10 ml. of ether, dry at 100° for 30 minutes and weigh the crucible. Filter the precipitated cuprous oxide through the crucible, wash the residue on the filter with hot distilled water, then with 10 ml. of alcohol, and then with 10 ml. of ether, and dry at 100°. The weight of cuprous oxide does not exceed 0·155 g., corresponding to not more than 0·5% of invert sugar.

Invert Sugar Syrup. A non-fermentable syrup with sugar content of 80% (26% to 45% invert sugar and 52% to 35% cane sugar) to replace *B.P. Syrup*. It has a higher gravity, 1·4 against 1·33, does not crystallise and retains brilliant appearance. Costs 50% more than ordinary syrup, but contains 20% more sugar. The taste is sweeter and less cloying. It does not cake so readily. It contains sucrose as well as dextrose and lævulose.—W. A. Whatmough, *Chem. & Drugg.*, i/1927, 281.

DIATOMITE

Diatomite (*B.P.C.* '34). Purified kieselguhr from diatomaceous or infusorial earth. Moisture limit (on ignition), 10%. Ignited acid-soluble residue, not more than 1%. *Terra Silicea Purificata, U.S.P. X*, is required to comply with the same limits for moisture and acid-soluble residue as the *B.P.C.* '34 substance.

Kaolinum (*B.P.* '32). Loss on ignition at a red heat, not more than 15%. Residue after ignition of the acid-soluble matter, not more than 1%. Kaolinum, *N.F. V*, leaves not less than 85% of non-volatile residue on ignition.

Talcum Purificatum (*B.P.C.* '34). Loss on ignition at red heat, not more than 1%. Water-soluble residue, not more than 0·1%. Ignited acid-soluble residue, not more than 0·5%. The *U.S.P. X* substance is allowed 5% loss on ignition.

Sodium Silicate, Solution of. *Syn.* Soluble Glass, Water Glass. A viscid solution usually containing 10% of caustic soda and 20% of silica. *Liquor Natrii silicici, P.G. VI*, has a sp. gr. of 1·296 to 1·396. The solution will arrest the putrefaction of organic matter. In powder form, this silicate is used medicinally in France, but both it and silica would appear to be unsuitable chemicals for use *per os*.

Potassium Silicate, Solution of. *Syn.* Soluble Glass. This was the original preparation. It is less viscid than the sodium compound and is also used to impregnate bandages for treating fractures.

DIGITALIS

Digitalis Folium (*B.P.* '32). Should contain not more than 2% of foreign organic matter, lose not more than 8% at 100°, and leave not more than 5% of acid-insoluble ash. *Digitalis, U.S.P. X*, contains not more than 2% of browned leaves, stems, flowers, or foreign organic matter; acid-insoluble ash, not more than 5%; in the form of the officially prepared tincture, it has a minimum systolic dose not exceeding 0·006 ml. of tincture, corresponding to 0·0000005 g. of ouabain for each gramme body weight of frog. *Folium Digitalis, P. Helv. V*, consists of the leaves of *Digitalis purpurea* Linn., collected when dry, dried immediately at 40° and then for 30 minutes at 55° to 60°. Moisture, not more than 1%; ash, not more than 10%; acid-insoluble ash, not more than 4%. Powdered digitalis consists of the powder of the whole leaf prepared without any residue and is not standardised biologically or chemically.

Digitalis Lanata. The leaves of *Digitalis lanata* Ehrh. have become a regular article of commerce; their physiological activity has been investigated by a number of workers, and the results published show that they have an activity which is from two to five times as great as that of the leaves of *D. purpurea* Linn. The following characters enable the leaves to be distinguished from those of *D. purpurea*. The cells of both epidermises have anticlinal walls which are distinctly beaded. The non-glandular trichomes are uniseriate, consistin

usually of from 10 to 14 cells; they are confined almost exclusively to the margins of the leaves. The paucity of the non-glandular trichomes causes the leaves to appear almost glabrous. Water pores occur singly or in groups consisting commonly of two pores.—T. Dewar, *Quart. J. Pharm.*, 1934, 331.

Cultivation. The late Dr. Martindale was of the opinion that a dry season favours potency, and he found that the most potent leaves, both chemically and physiologically, were second-year leaves from plants grown in England in sunny exposed position, the plants showing no flower spikes at the time of collection. He pointed out that all second-year plants do not necessarily flower and that more stress should be laid on the sunny situation than on the point of non-flowering at the time.

The petioles and midribs of the leaves contain less of the active principles than the lamina—they can be removed by sifting. Heavy seed should be used for cultivation.

Constituents. Digitalis contains several glycosides, to which its physiological activity is due; of these, digitoxin, $C_{41}H_{64}O_{13}$, and gitoxin, $C_{41}H_{64}O_{14}$, have been obtained crystalline. A third glycoside, $C_{47}H_{74}O_{18}$, is described as having the composition of digitoxin with the addition of one molecule of dextrose; it is hydrolysed by the enzymes of the leaf into digitoxin and dextrose. The remaining glycosides have not been obtained in a state approaching purity; they are amorphous and more soluble than the crystalline glycosides. The latter are very sparingly soluble in water, but become more soluble in the presence of the amorphous glycosides. Distinctive names have been given to various mixtures, but only the two above-mentioned glycosides are definite substances. Gitalin and digitalein are mixtures of indefinite composition. Anhydrogitalin is a crude form of gitoxin. Digitalis seeds do not contain digitoxin or gitoxin, but contain a closely-related glycoside, digitalinum verum, $C_{36}H_{56}O_{14}$, associated with a large proportion of water-soluble glycosides and two physiologically-inactive glycosides, digitonin, $C_{55}H_{90}O_{29}$, and gitonin, $C_{49}H_{80}O_{28}$. Digitalinum verum is not crystalline, but it forms crystalline derivatives. A standardised mixture of glycosides prepared from the seeds is known as digitalin, or digitalinum purum germanicum.

A preparation of the glycosides representing about 74% of the total activity of the original leaf may be obtained by extracting the leaf with benzene. The residue is extracted with alcohol, and benzene added followed by water. The aqueous-alcoholic layer is concentrated by means of chloroform followed by precipitation of the glycosides with light petroleum.—E. Hesse, W. Altner and J. Becher, *Klin. Wschr.*, 1933, 12, 1862.

Fresh concentrated infusions made with 20% alcohol or 0.1% chloroform in water are essentially digitoxin preparations, whereas the fresh B.P. infusion is a digitalein preparation. Old concentrated infusions showed absence of therapeutic value in the filtrate with presence of toxic effects, the sediment being also toxic and possessing tonic effect.—K. Samaan, *Pharm. J.*, i/1921, 481.

Martindale's Chemical Assay for Digitalis.

The determination of the value of a digitalis preparation (especially the tincture) by chemical means is fraught with considerable difficulties owing to many factors, e.g., the numerous glycosidal bodies contained, the fact that it is not possible to point to one glycoside as the potent constituent responsible for the activity of the drug, and again, the extraction of the substances in any degree of purity requires some analytical skill.

A tincture having by physiological tests a m.l.d. calculated as 0.75 ml. per 100 g. weight of frog was adopted as a standard.

In a paper read before the Pharmaceutical Society of Great Britain, Dec. 10, 1912, the results of examination were provided of a number of samples of leaves from various parts of the world (Great Britain, Germany, Italy, India, etc.). Almost all of these leaves gave tinctures of standard, or above standard, strength. (The paper was later published in a booklet entitled "*Digitalis Assay*.")

The colorimetric method devised was claimed by Martindale to give results equivalent to the physiological assay method based on the minimum lethal dose required to kill a frog and calculated to 100 g. body weight. The method requires some care in carrying out, as it is strictly quantitative. It is as follows:—

To determine whether a tincture is up to physiological test requirements (usually taken at m.l.d. = 0.75 ml. per 100 g. body weight of frog) mix 10 ml. of the tincture with 10 ml. of water, precipitate with 10% neutral lead acetate solution (about 3 ml.), adding a little diatomite. Allow to stand for

15 minutes, filter off on the pump and wash the precipitate slightly. Remove excess of lead from the filtrate with 10% sodium phosphate solution (about 2 ml. required) and filter. Add a little calcium carbonate (about 0.2 g.) to the filtrate (to prevent possible hydrolysis of the glycosides), and evaporate to dryness on a water-bath. Add about 2 g. of dry washed sand to the residue and extract with chloroform five times by thorough trituration, using about 10 ml. on each occasion. Filter and evaporate the chloroformic solution and extract the residue with warm water on the water-bath, using 10 ml. and 5 ml. and again employing sand. Filter, evaporate to dryness in a porcelain basin, extract the residue again with cold chloroform to purify it (about three or four quantities of 5 ml. each, using dry sand and triturating thoroughly with a small pestle) and filter. Evaporate the combined chloroformic liquors and dissolve the residue in 4 ml. of glacial acetic acid. Mix 0.1 ml. of this acetic solution with 1 ml. of sulphuric ammonium molybdate reagent in a 5 × 1 cm. test-tube and compare the depth of colour after five minutes with that produced with 10 ml. of the standard tincture, mounting the tubes on a little slab of plasticine and observing the colours by direct transmitted light using a white background. This coloration indicates the *content of combined "active water-soluble" glycosides* (probably including digitoxin). Further, if 0.1 ml. of the acetic solution be mixed with 0.5 ml. of glacial acetic acid, and this be layered upon 1 ml. of the sulphuric ammonium molybdate reagent, the typical blue ring showing presence of digitoxin should be formed.

Chemical assay processes used in the past centred on an estimation of the digitoxin—*ignoring the bodies which are known to be readily soluble in water*. That this was fallacious was shown by Ziegenbein, who found that leaves containing only 0.125% of this glycoside were twice as active as those containing 0.226%.

The above method includes the latter in addition to digitoxin or an allied body. The process includes a strong indication of digitoxin—either through the actual solubility of it in the repeated quantities of solvent (the amount of digitoxin in 10 ml. of tincture is extremely minute though sufficient to detect) or owing to the fact that digitoxin is soluble in the presence of the other glycosides and saponins. Results approximating the physiological m.l.d. results were obtained with the samples of tinctures referred to, even after 12 months storage.

Tschirch confirms Ziegenbein's findings that the digitoxin content in digitalis leaves is not in proportion to the physiological activity. It was found that *chloroform must be used repeatedly* (eight shakings) to remove the entire active substances. Absolute alcohol, acetone and amyl alcohol will exhaust leaves completely; chloroform, acetic ether and benzene partially. Ether and carbon tetrachloride do not extract the active substances at all. Acetone is especially good as yielding a colourless extractive. It can be used for assaying. (The use of acetone instead of chloroform in Martindale's method might yield interesting results.)—Tschirch & Wolter, *Schweiz. ApothZtg.*, 56, 469; per *Pharm. J.*, i/1919, 219.

A comparison of the results of the biological assay and the colorimetric assay of Knudson and Dresbach on nine samples of leaves from 4 different species showed very close agreement. In the colorimetric process referred to, the infusion of the sample is precipitated first with lead acetate and then with sodium phosphate, and the filtrate is treated with sodium picrate. The colour produced is compared with that given by a standard solution of ouabain. In place of the latter, the authors used a solution of potassium dichromate.—B. J. Oikeloën and J. C. Timmer, *Pharm. Weekbl.*, 1931, 68, 820.

Method found unreliable.—J. A. C. Pinxteren, *ibid.*, 1932, 69, 4.

Only one out of fifteen samples assayed by the method of Knudson and Dresbach agreed with the biological (frog) assay.—F. J. Dyer, *Quart. J. Pharm.*, 1932, 172.

Digitalis Pulverata (B.P. '32). Adjusted for therapeutic administration to contain 10 units in 1 g. Loss at 100°, not more than 8%.

BIOLOGICAL METHODS OF ASSAY

The potency of powdered digitalis, B.P., is determined by comparing each sample with a standard preparation of powdered digitalis which is distributed by the National Institute for Medical Research, Hampstead. The strength of the standard preparation has been carefully determined by comparison with the international standard digitalis powder, which is equal in potency to the average potency of powdered digitalis. When an unknown sample has been

compared with the standard preparation, its potency can then be expressed in terms of the international standard, that is to say, a statement can be made as to how much stronger or weaker the sample is than an average sample. To make this statement short, the international standard is arbitrarily described to contain 10 units of activity in 1 g. A sample which is 1.4 times as strong then contains 14 units per g.

Samples of powdered digitalis for therapeutic administration must be adjusted to contain 10 units per g. The maximum dose for repeated use is given as 0.1 g., or 1.5 grains, which is 1 unit, while the maximum single dose is 0.6 g., or 10 grains, which is 6 units. *B.P.* '32 permits any method of assay to be used which is based on the effect of digitalis on cardiac muscle, or which gives results parallel to those obtained on cardiac muscle. *B.P.* '32 suggests the frog method and gives instructions for performing it.

The Frog Method. The standard preparation and the unknown sample are extracted by a suitable method, for example tinctures of each are prepared with 70% alcohol. The tinctures, diluted with saline, are injected into two groups of frogs, which are as nearly as possible alike. The proportion of frogs killed in 24 hours by a given dose of the standard tincture and the proportion killed by a given dose of the unknown are then determined. Now, the relative potency of doses killing different proportions of frogs has been investigated on large numbers of frogs (Trevan, *Proc. roy. Soc.*, Ser. B, 1927, 101, 483) and a table showing these relative potencies is given in *B.P.* '32. For example, if the dose which kills 50% is taken as 100, then experiment has shown that the dose killing 30% is 87. By means of this table the potency of the unknown tincture is related to that of the standard. *B.P.* '32 requires that not less than 50 frogs be used in the comparison, since the standard deviation, that is to say the error in two-thirds of the tests, will then not be greater than 10%. Likewise, the error in twenty-one out of twenty-two tests will not be greater than 20%.

The South African clawed frog or toad, *Xenopus laevis*, was found to respond more constantly than species of *Rana* to the digitalis series of drugs and is recommended for use in the biological assay of digitalis.—J. W. C. Gunn and D. Epstein, *Quart. J. Pharm.*, 1932, 180.

The Cat Method. The cat method differs from the frog method in that the minimum lethal dose for each cat is determined. Much confusion has arisen due to the incorrect use of this term; when a single dose of digitalis is injected into a frog, or of another drug into another animal, the animal either dies or survives, and it is impossible to say whether the dose was the minimal lethal dose or not; it is only possible to discover with accuracy the dose killing a certain proportion of animals, for none of which it may be minimal. The term L.D. 50 was introduced by Trevan to indicate the "mean lethal dose" which kills 50%. The expression "minimal lethal dose" should be reserved for those estimations in which the least amount of a substance necessary to kill is actually determined, of which the administration of digitalis to a cat is an example. As in the frog method both the standard preparation and the unknown sample of powdered digitalis are extracted by a suitable method; a 0.5% hot water infusion (90° for 15 minutes) is convenient. The extract is placed in a burette from which it is allowed to flow at a slow constant rate into the vein of an anaesthetised cat. The time of inflow is usually from 30 to 45 minutes, at the end of which period a concentration of the digitalis glycosides reaches the heart sufficient to produce arrest in systolic contraction. Throughout the experiment the cat is given artificial respiration to ensure that death does not occur from respiratory failure. The amount of extract administered up to the time of cardiac arrest is recorded, and a calculation made to determine the amount per kg. body weight. The figures for a series of cats are obtained both for the standard extract and for the unknown extract. *B.P.* 1932 requires that the standard extract be tested on 14 cats and the unknown on 6 cats; with these numbers the error of the estimation is then about the same as in the frog method. The test of the standard extract is not repeated each time an unknown extract is tested; it is sufficient to test the standard extract once a year, as cats do not vary in sensitiveness at different times. The average minimal lethal dose of a 0.5% hot water infusion of the international standard digitalis powder is 18.0 ml. per kg. cat. This corresponds to 90 mg. per kg. of the powder itself, but the figure varies according to the composition and amount of the anaesthetic used. (See Macdonald, *Quart. J. Pharm.*, 1934, 182.) While 90 mg. per kg. is the figure for cats under light anaesthesia with ether, 75 mg. per kg. is the figure for cats fully anaesthetised with ether.

Ether is an unsuitable anæsthetic for use in the assay of digitalis by the cat method in the tropics, but identical results are obtained when other anæsthetics are used, provided an uninterrupted and uniform depth of anæsthesia can be obtained without any side-effects on the circulation or respiration.—J. C. David and N. Rajamanickam, *Quart. J. Pharm.*, i/1934, 36.

HATCHER CAT UNIT. Hatcher defined the cat unit of powdered digitalis as the average minimal lethal dose per kg. Thus 1 cat unit of the International Standard digitalis powder can be taken as 90 mg., but as seen from the foregoing paragraph, it depends on the amount of anæsthetic. Since 1 international unit is by definition the amount of activity in 100 mg. of the international standard digitalis powder, it may be said that the relation between the Hatcher cat unit and the international unit is 9 to 10, but the relation varies according to the technique of each laboratory.

POTENCY IN INTERNATIONAL UNITS. If the average minimal lethal dose for the 0.5% hot water infusion of the standard is found to be 16 ml. per kg., and if the figure for a similar extract of the unknown sample is 14 ml. per kg., then the potency of the unknown sample is $\frac{16}{14} = 1.14$ times that of the standard. If

the standard preparation is exactly equal to the international standard digitalis powder, then the unknown sample of powdered digitalis contains 11.4 units per g.

Guinea-pig Method. The *B.P.* '32 mentions the method of intravenous injection into guinea-pigs, which is in essentials similar to the cat method. It was introduced by Knaffl-Lenz (*J. Pharmacol.*, 1926, 29, 407). Animals weighing 400 g. to 700 g. are anæsthetised with urethane, 1.75 g. per kg., injected under the skin. The digitalis extract, in concentration of 1.25%, is allowed to enter the jugular vein at constant rate. The experiment takes about 20 minutes. The method has the advantage that guinea-pigs vary less in sensitiveness to digitalis than cats, and a smaller number give the same accuracy. The *B.P.* '32, however, requires the same number of guinea-pigs as of cats.

Pigeon Method. When one of the cardiac glycosides is injected into the vein of a pigeon, it vomits in the course of 10 to 15 minutes, provided the dose is sufficient. (Hanzlik, *J. Pharmacol.*, 1929, 35, 363; also Burn, *ibid.*, 1930, 39, 221.) Powdered digitalis may be assayed by preparing a tincture and comparing it with a tincture prepared from the standard preparation. A dose of the order of 0.2 ml. of tincture per kg. is injected, the tincture being diluted so that the volume given to a bird weighing 300 g. is about 0.3 ml. The dose is given to each of a group of about twenty-five birds, and the proportion which vomit is observed. This proportion is determined both for unknown and for the standard. The relative potency of unknown and standard is then calculated from data previously obtained. (See Burn, *loc. cit.*)

United States Pharmacopœia X Method. The requirement for digitalis *U.S.P. X*, is that when injected in the form of tincture into frogs, the minimum systolic dose per gramme body weight of frog must not exceed 0.006 ml. which is stated to be equivalent to a dose of 0.0000005 g. ouabain per g. body weight. Thus the *U.S.P.* takes the crystalline glycoside from *Strophanthus gratus* as a standard for digitalis and directs that a tincture prepared from the leaf shall be compared with this standard by finding the minimum systolic dose; this dose is the smallest dose which causes arrest of the heart of the frog in one hour. The requirement may be criticised because it makes two assumptions (1) that variation in the resistance of frogs to digitalis runs parallel to variation in the resistance to ouabain, (2) that a dose of 0.006 ml. per g. of a good tincture will always be sufficient to cause arrest of the frog heart in one hour.

Tincture of Digitalis.

(a) ***B.P.* 1932.** 1 ml. must contain 1 unit of activity. The assay is performed by comparing the tincture with a tincture prepared from the standard preparation (*B.P.* '32) by one of the methods described for powdered digitalis. The tincture is usually prepared to contain more than 1 unit per ml.; it is then assayed and diluted to exactly 1 unit per ml.

(b) ***U.S.P. X.*** The minimum systolic dose must be not less than 0.0055 ml. and not more than 0.0065 ml. of tincture per g. body weight injected into frog, these doses being equivalent to a minimum systolic dose of not less than 0.00000046 g. or more than 0.00000054 g. of ouabain per g. body weight. (See requirement for Digitalis.)

Digitalinum (*B.P.C.* '34). Possesses 80 units of activity in 1 g. (equivalent the activity of 8 g. of the international standard digitalis powder). Assayed biologically by the *B.P.* process for *Digitalis Pulverata*.

Kiliani Test for Digitalin. Ferric sulphate, 0.05 g., is dissolved in water; 1 ml., and sulphuric acid added to 100 ml. Employed as a mixing test (0.1 mg. of the glycoside is sufficient, dissolved in 0.2 ml. of glacial acetic acid), this reagent produces a pink colouration.

This test with digitoxin produces a brownish colour.

Assay. Digitalin is assayed by one of the methods described for powdered digitalis, in comparison with the standard preparation described in *B.P.* '32. Gage (*Quart. J. Pharm.*, 1933, 161) has found that unstandardised samples vary from 50 to 55 units per gramme. The dose given in *B.P.C.* for the standardised digitalin is $\frac{1}{2}$ to 1 grain for single administration; this corresponds to 2.5 to 5 units; it is injected subcutaneously or intramuscularly, being the only digitalis body which can be given in this way.

Digitoxinum (*B.P.C.* '34). M.p., not below 240°. Loss at 100°, not more than 1%.

Keller-Kiliani (Syn. Keller's) Test for Digitoxin in the Leaves.

Shake 10 ml. of filtered infusion in boiling water, 1+20, in a separator for a few minutes with chloroform, 10 ml., add ether, 5 ml., and alcohol, 5 ml.; shake again and filter off the chloroform-ether solution through a filter moistened with chloroform. The liquid is evaporated and the residue dissolved in 3 ml. of acetic acid (96%). A drop of diluted solution of ferric chloride (1+19) is added, and the whole, in a narrow test-tube, is layered carefully upon sulphuric acid; at the point of contact of the two liquids a brownish-red zone develops, and over it a bluish-green zone.—*P.G. V.* It has been found in practice that the presence of chlorophyll hinders the coloration considerably.

The test may also be applied to the glycosidal substance *Digitoxin* thus:—Dissolve 0.001 g. in 3 ml. of glacial acetic acid, add a few drops of the ferric chloride solution and proceed exactly as described above.

Froehde's Test (sulphuric ammonium molybdate, see colorimetric method above). Ammonium molybdate, 1% *w/v*, in concentrated sulphuric acid used as a *mixing* test gives characteristic maroon colour with the water-soluble glycosides. Used as a layering test, it gives a characteristic blue ring.

There is no standard in *B.P.* '32 or in *U.S.P. X* for digitoxin. Gage (*Quart. J. Pharm.*, 1934, 654) has examined a series of commercial samples in comparison with the standard preparation for powdered digitalis (*B.P.*) by two biological methods, the frog method and the guinea-pig method, and found that their activity varied from 900 to 1200 units per gramme. A pure crystalline sample of Digitaline Nativelle had a potency of 1500 units per gramme.

Digoxin. A crystalline glycoside from *Digitalis lanata* which can be given by mouth or by intravenous injection. Its potency has been determined by White (*J. Pharmacol.*, 1934, 52, 1) on various species. On the cat and the frog it has about one quarter of the activity of ouabain, and probably contains about 2500 units per gramme. It exerts a cumulative effect when administered by mouth to cats or guinea-pigs.

Assayed biologically by the frog method, 0.6 mg. of digoxin was equivalent to 1 ml. of standard tincture, whereas when assayed by the cat method the equivalent amount was 0.4 mg. Administered orally to patients with auricular brilliancy, single doses of 1 to 2 mg. produced a rapid fall in ventricular rate, and the average subsequent daily dose found necessary was 0.5 mg. It is not necessary to administer digoxin by injection except in exceptional cases.—*J. J. Wayne, Cli. Sci.*, 1933, 1, 63.

EPHEDRA

Ephedra (*B.P.C.* '34). Contains not less than 1.25% of total alkaloids calculated as $C_{10}H_{15}ON$. Assayed by the *B.P.C.* '34 process as follows:—Add 200 ml. of ether-chloroform (3 : 1) to 10 g. of the powdered drug, and after 5 minutes, add 10 ml. of dilute solution of ammonia and 1 g. of anhydrous sodium carbonate, shaking frequently for four hours and standing overnight; after percolation to exhaustion with 100 ml. of ether-chloroform

and then with ether, extract the percolates with N/3 hydrochloric acid, nearly neutralise the filtered acid extracts with N/1 sodium hydroxide, add 10 g. of anhydrous sodium carbonate and salt saturation, and extract with ether; allow the decanted, filtered ether extracts to evaporate spontaneously, dissolve the residue in excess of N/10 sulphuric acid and back titrate with N/10 sodium hydroxide to methyl red.

Ephedrina (*B.P.C.* '34). $C_{10}H_{15}ON = 165.1$. M.p., not below 35° . Specific rotation on a 2% *w/v* solution in carbon dioxide-free water, not less than $+12.5^{\circ}$. Ash, not more than 0.1%.

Ephedrinæ Hydrochloridum (*B.P.* '32). $C_{10}H_{15}ON, HCl = 201.6$. M.p. 217° to 220° . Specific rotation in 5% *w/v* aqueous solution, -33° to -36° . Loss at 100° , not more than 0.5%, and ash, not more than 0.1%.

Ephedrinæ Sulphas (*B.P.C.* '34). $(C_{10}H_{15}ON)_2, H_2SO_4 = 428.3$. Specific rotation on a 10% *w/v* aqueous solution, -30° to -31.6° . Loss at 100° , not more than 0.5%. Ash limit, 0.1%.

Quantitative methods for the determination of ephedrine in inhalants and tablets are described in *Methods of Analysis* (*A.O.A.C.*, 1930, 455).

ERGOTA

Ergota (*B.P.* '32). Should contain not less than 2% of foreign organic matter, and not less than 0.05% of total alkaloids, calculated as ergotoxine. Assayed by digestion of the powder defatted with cold light petroleum (b.p. 40° to 60°) and dried below 40° , with anæsthetic ether, with the addition of magnesium oxide diffused in water; after clearing with tragacanth and filtering, an aliquot part is extracted with four portions of 1% tartaric acid solution; 1 volume of the mixed acid solutions, previously adjusted to volume, is mixed with 2 volumes of dimethylaminobenzaldehyde solution, warmed to 45° and exposed to bright light for from 10 minutes to 2 hours, matching the blue-violet colour produced with a standard solution of ergotoxine ethanesulphonate similarly treated.

Ergota, *U.S.P. X*, contains not more than 5% of seeds, fruit or other foreign organic matter and is standardised biologically (See below.) *Secale cornutum*, *P.G. VI*, assayed by the process prescribed, contains not less than 0.05% of the water-insoluble alkaloids of ergot.

In the *B.P.* colorimetric test a 0.125% solution of dimethylaminobenzaldehyde in 65% *v/v* sulphuric acid and containing 0.005% of $FeCl_3$ may be used instead of the official solution in 50% *v/v* sulphuric acid. No heating is required, and the full colour is produced within one minute without special exposure to strong light.—N. L. Allport and T. T. Cocking, *Quart. J. Pharm.*, 1932, 341.

Allport and Cocking's modified reagent gives results identical with those given by the official method.—E. M. Smelt, *Quart. J. Pharm.*, 1933, 399.

The use of a colorimeter is not essential. Dilute the solutions about ten times with water and compare the colours in Nessler glasses.—P. A. W. Self, *Pharm. J.*, i/1933, 245.

The effect of hot solvents on original ergot has been investigated. Ethyl dichloroethylene, trichloroethylene and benzene have been found to extract the major portion of the alkaloids; light petroleum does not extract the alkaloids.

In the case of dichloroethylene and benzene, quantitative recovery of the alkaloids has been made, proving that the alkaloids are extracted and not destroyed by the solvents.—R. F. Corran and F. E. Rymill, *Quart. J. Pharm.*, 1935, No. 3.

BIOLOGICAL METHODS OF ASSAY

There is no biological method of estimating ergotoxine by which the error is less than 50%.

U.S.P. X Method. Ergot and fluidextract of ergot are assayed by the cock's comb method. When an extract of ergot is injected into the breast muscles of a cock, the ergotoxine present causes a darkening of the colour of the comb. The darkening is first seen in the hindmost part of the comb, and, according to the amount of ergotoxine, spreads forward. An unknown sample of fluidextract is compared with a standard fluid extract which is distributed by the U.S. Dept. of Agriculture. From 5 to 10 cocks of about 2 kg. weight are used for the comparison, and receive doses varying from 0.25 ml. to 0.5 ml. The combs of birds which have been injected with the sample are then compared with those injected with the standard. A dose of 0.25 ml. of the standard fluidextract is stated to be equivalent to 0.2 mg. of ergotoxine base, from which the standard fluid extract must be equivalent to 0.08% of ergotoxine. A sample standard fluid extract tested by the rabbit uterus method at the Pharmaceutical Society's Laboratories was found to be equivalent to 0.03% of ergotoxine. From 1st May, 1935, a standard sample of ergotoxine ethanesulphonate is to be used as the standard for assaying ergot and fluidextract of ergot by the cock's comb method. Ergot is required to possess a potency per gramme equivalent to not less than 0.5 mg. of the official standard ergotoxine ethanesulphonate. The fluidextract is required to contain the equivalent of not less than 0.4 mg. and not more than 0.65 mg. per ml.—*U.S.P. Interim Revision, Announcement No. 3, January, 1935.*

Rabbit Uterus Method. A method which has been widely used for estimating the ergotoxine present in ergot extracts was described by Broom and Clark (*J. Pharmacol.*, 1923, 22, 59). When strips of the uterus of a rabbit are suspended in a bath of oxygenated Ringer's solution at 37°, the strips contract when adrenaline is added to the bath. If ergotoxine is added to the bath, the power of the strip to respond to adrenaline soon disappears, according to the concentration of ergotoxine and the time it is allowed to act. To estimate the ergotoxine present in an extract, two strips are cut from the same piece of uterine muscle and suspended in baths placed side by side. The response to a given dose of adrenaline is recorded for each strip, and when fresh Ringer's solution has been placed in each bath a dose of ergotoxine is added to one bath and a dose of the unknown extract is added to the other. After an interval which must be the same for each bath, and may be 8 or 10 minutes, the dose of adrenaline is added again. The response is now reduced, and is reduced by the greatest amount in that bath in which most ergotoxine is present. By making observations on many pairs of strips, a figure can be obtained for the amount of ergotoxine in the extract, but the method is tedious and is subject to a large error.

A biological method for the assay of ergot is described in *Methods of Analysis* (I.O.A.C., 1930, 487).

Ergota Præparata (*B.P.* '32). Contains from 0.08% to 0.12% of total alkaloids of ergot, calculated as ergotoxine.

Extractum Ergotæ (*B.P.C.* '34). When freshly prepared, contains 0.5% of total alkaloids, calculated as ergotoxine.

Extractum Ergotæ Liquidum (*B.P.* '32). Assayed by extracting the diluted extract, made ammoniacal, with anæsthetic ether, shaking the ether with tartaric acid solution and proceeding as for the assay of Ergota, it contains when freshly prepared 0.06% *w/v* of total alkaloids, calculated as ergotoxine; after storage it contains not less than 0.04% *w/v*. Fluidextractum Ergotæ, *U.S.P. X*, produces a darkening of the comb, when injected intramuscularly in single-comb, white Leghorn cocks, corresponding to that produced by the corresponding dose of the standard ergotoxine ethanesulphonate (see above).

The colour with *p*-dimethylaminobenzaldehyde is given also by the pharmacologically inactive alkaloids ergotinine and ψ -ergotinine which are present in fluid extract of ergot. About 60% to 70% of the total alkaloids consists of ergotoxine and the standard of 0.05% of total alkaloids corresponds therefore to about 0.03% of ergotoxine.—*Rep. of Pharmacopæia Sub-Committee on Ergot*, October, 1931.

Stability. When diluted in a mixture it will lose all activity in 2 or 3 days, but if stored in completely filled unopened bottles the loss of activity during 6 months is inappreciable.—*B. A. Bull, Pharm. J.*, i/1933, 317.

If the liquid extract is kept under ordinary dispensary conditions for more than six weeks the strength is likely to fall below the *B.P.* limit. The keeping properties are much improved by storage in full bottles in the dark, and the deterioration in an ice-chest is very slow.—E. M. Smelt, *Quart. J. Pharm.* 1933, 399.

On dilution with water, it yields a precipitate which contains the greater part of the alkaloids. The loss in strength is about 30% in 10 to 14 days. When dispensed with other substances the rate of loss of activity differs with different extracts but is usually more rapid. Ferric chloride greatly increases the loss of activity.—E. F. Hersant and W. H. Linnell, *Pharm. J.*, ii/1933, 3.

Ergotoxina (*B.P.C.* '34). Specific rotation, determined on a 2% *w/v* solution of the anhydrous substance in chloroform, not less than -180° . On drying *in vacuo* at 90° it loses not more than 5%. At 190° to 200° the substance decomposes with evolution of gas. Ash limit, 0.1%.

Ergotoxinæ Æthanosulphonas (*B.P.* '32). Specific rotation, determined on a 4% *w/v* solution of the anhydrous substance in acetone and water (2 : 1 by volume), $+112^\circ$ to $+122^\circ$, and of the separated anhydrous base, the same as specified for Ergotoxina. The anhydrous salt contains acid equivalent to 16.1 to 16.7% of ethanesulphonic acid. Loses *in vacuo* at 90° to 100° not more than 5%. Ash limit, 0.1%.

Ergotamine. Ergotamine is less active biologically than ergotoxine but is approximately equivalent when examined colorimetrically. If used as a standard in the biological assay of ergot, 60% of the observed readings gives a close approximation of the ergotoxine content. A similar correction should be applied in the colorimetric assay of ergot owing to the biological inactivity of ergotinine.—E. Lozinski, G. W. Holden and G. R. Driver, *Quart. J. Pharm.*, 1933, 395.

NEW CONSTITUENTS OF ERGOT.

Chassar Moir (*Brit. med. J.*, i/1932, 1119) has shown that the liquid and solid extracts of ergot of the *B.P.* '14, when administered orally, show marked activity in stimulating the puerperal uterus. The effect comes on rapidly and is not very prolonged, thus differing from the effects produced by ergotoxine and ergotamine. This activity is also possessed by the *B.P.* '32 liquid extract. In a subsequent paper, H. W. Dudley and Chassar Moir (*Brit. med. J.*, i/1935, 520) recorded the isolation of the active principle, apparently an alkaloid, responsible for this effect and named it **Ergometrine**. The yield from 10 kg. of defatted ergot was 0.82 g. In oral doses of 0.0005 to 0.001 g., ergometrine provoked uterine contractions in from $6\frac{1}{2}$ to 8 minutes. For intramuscular injection an adequate dose is 0.00025 to 0.0005 g., and intravenously, 0.00005 to 0.0001 g. The alkaloid is soluble in organic solvents, can be extracted by weak alkali and gives the colour reaction with dimethylamine benzaldehyde. Simultaneously with the announcement of the isolation of ergometrine, M. E. Davies et al. (*Amer. J. Obstet. Gynec.*, i/1935, 155) reported the discovery of a new ergot alkaloid effective when administered orally; this being supplied commercially (in America) under the name **Ergotocin**. A further account of the isolation and properties of an ergot alkaloid active when administered orally is given by M. R. Thompson (*J. Amer. pharm. Assoc.* 1935, 185).

Ergometrine is prepared by the following process:—1 kg. of defatted powdered ergot is moistened with 1.5 litres of absolute methylated alcohol (5% methyl alcohol) to which 50 ml. of 0.88 ammonia has been added. The whole material is extracted in a percolator with absolute methylated alcohol. After about 3 litres of percolate have been collected, the extract is evaporated to about 200 ml. in a vacuum, the water-bath temperature being kept at 40° to 45° .

To this concentrate are added about 300 ml. of 0.25 N sulphuric acid (sufficient to render the reaction faintly acid to congo-red), and the distillation is continued until all the residual alcohol has been removed. Fat separates as the concentration of alcohol decreases. The fluid is then chilled at about 2° , when most of the fat becomes hard enough to be removed mechanically.

After filtration through paper, the acid aqueous solution, measuring 200 to 250 ml., is treated with saturated aqueous sodium carbonate solution (about 10 ml.) until the reaction is very faintly alkaline to litmus. It is then filtered from the flocculent precipitate which is produced, made alkaline by the addition of more saturated sodium carbonate solution (about 20 ml.) and extracted five times with 50 ml. quantities of chloroform. The chloroform extract is freed from watery droplets, carried over mechanically, by shaking with a small quantity

hydrous sodium carbonate, filtered, and evaporated in a vacuum (water-bath 45° to 50°). As the solution is concentrated, crude crystalline ergometrine separates. The volume is reduced to from 5 to 10 ml. After keeping at 2° for an hour the crude ergometrine is collected on a filter and washed with a little chloroform. Suitable solvents for the recrystallisation of ergometrine are benzene, acetone, ethyl acetate, and methylethyl ketone; after adequate recrystallisation, e.g., from methylethyl ketone, it melts and decomposes at 161° to 162°. The yield from defatted Spanish ergot was 0.2 g. per kg.—H. W. Audley, *Pharm. J.*, i/1935, 709.

The purest specimen of ergometrine obtained, exhibiting an E value of 185 and melting at 164°, gave a colour by the chemical test equivalent to that produced by 1.78 times its weight of ergotoxine base. Ergometrine in aqueous tartaric acid solution shows an absorption band in the ultra-violet region with a maximum at 316 m μ . The same band is exhibited by solutions of ergotoxine. The colour produced when ergometrine is submitted to the *p*-dimethylamino-benzaldehyde test is spectroscopically identical with that produced by ergotoxine under the same conditions.—N. L. Allport and Sydney K. Crews, *Quart. J. Pharm.*, 1935, No. 3.

EXTRACTUM HEPATIS

Extractum Hepatis Siccum (*B.P.* '32). Should contain not less than one-tenth its weight of sodium chloride and should be packed in tubes, each containing the equivalent of 225 g. of original liver.

Extractum Hepatis Liquidum (*B.P.* '32). 1000 ml. should contain the equivalent of 8000 g. of original liver, not less than the equivalent of 10% *v/v* of 95% alcohol, and not less than 20% *v/v* of glycerin.

EXTRACTUM MALTI

Extractum Malti (*B.P.* '32). Determined by the Kjeldahl method, it contains nitrogen equivalent to not less than 4.5% *w/w* of protein. Sp. gr., 1.40 to 1.42. n_{D20° , 1.4892 to 1.4976. **Extractum Malti, U.S.P. X**, should be capable of converting not less than five times its weight of starch into water-soluble sugars; assayed by testing for remaining starch, with N/10 iodine, the resultant solution from a digestion of purified potato starch (equivalent to 5 quantities of dried starch) at 40° for thirty minutes.

Extractum Malti cum Oleo Morrhuae (*B.P.* '32). Contains 10% *w/w*, equivalent approximately to 15% *v/v*, of cod-liver oil.

Extractum Malti cum Vitaminis (*B.P.C.* '34). Each fluid drachm contains approximately 3000 units of Vitamin A and approximately 225 units of Vitamin D.

Methods of Analysis for All-English Malt Extracts. S.R. & O., 1933, No. 540.

(i) *Diastatic Activity (or Lintner Value)*

SOLUBLE STARCH. Digest purified potato starch with dilute hydrochloric acid of sp. gr. 1.04 (in the proportion of 1 lb. of starch to 1 litre of dilute acid) at a temperature not exceeding 20° for 7 days, well shaking daily. Thoroughly wash the starch by decantation, first with tap water until washings react only faintly acid, then four times with distilled water. Weigh about 20 g. of the sludge, dissolve in 200 ml. of boiling distilled water and neutralise with N/10 sodium hydroxide solution, using 2 or 3 drops of alizarin cream as indicator. Add to remaining weighed starch sludge the calculated amount of sodium hydroxide solution just to neutralise its acidity, shake thoroughly and set aside

for 12 hours. Wash by decantation three times with distilled water, collect the soluble starch on a paper in a Buchner funnel and drain by suction. Transfer to new unglazed porous plates and dry at moderate temperature (40° to 45°). When moisture content is reduced to about 15%, grind the soluble starch in a porcelain mortar and rub through a fine hair sieve.

SOLUBLE STARCH SOLUTION. Rub 20 g. of soluble starch into a cream with water and pour into about 700 ml. of boiling water. Bring to the boil and heat for a further 2 minutes, then cool to about 20°, shaking to prevent formation of skin. Add 20 ml. of acetate buffer solution (see below) and dilute to 1 litre with water. (10 ml. of this solution should not reduce 0.1 ml. of Fehling's solution). Fresh soluble starch solution should be made for each day's determination.

ACETATE BUFFER SOLUTION. One litre to contain 68 g. of sodium acetate ($\text{CH}_3\text{COONa} \cdot 3\text{H}_2\text{O}$) and 500 ml. of N/1 acetic acid.

MALT EXTRACT (SYRUP) SOLUTION. 5% solution. Weigh 10 g. of extra malt extract and break down with cold water. Heat must not be used to assist weighing or bringing into solution. Transfer the solution to a 200 ml. graduated flask, dilute to the mark at 15° and shake well. Weaker solutions, also made up at 15°, are prepared from this. These solutions must not be filtered and are used as soon as possible for starch conversion.

MALT EXTRACT (FLOUR SOLUTION). 5% solution. Weigh 10 g. of flour into a beaker, add 200 ml. of water at 15° and thoroughly stir. Cover and digest for 3 hours in a water-bath at 21°, stirring at intervals of half an hour. Three hours after, filter through filter paper. Reject the first 25 ml. of filtrate and if the remainder of the filtrate is not quite bright re-filter. This solution or weaker solutions prepared from it, is used as soon as possible for starch conversion.

METHOD OF STARCH CONVERSION. Measure 100 ml. of soluble starch solution into a 200 ml. graduated flask and immerse, suitably supported, in a water-bath maintained at 21°. Place a standardised thermometer in the flask and when the contents have reached 21° add, by means of a narrow-bore pipette (N.P.L. standard), a definite volume (which should not normally exceed 10 ml. measured at 15°, of the malt extract solution and mix well. (The volume needed will depend upon the diastatic activity of the extract and will be about

80

_____ ml. of 5% solution or correspondingly large
DIASTATIC ACTIVITY OF THE SAMPLE

volumes of 2½% or 1% solution.) Maintain the contents of the flask at 21° for exactly one hour. Then add 20 ml. of N/10 sodium hydroxide solution and mix immediately, care being taken to wash down the thermometer and also to allow the alkali to flow over the inner surface of the neck of the flask. Cool the solution to 15°, dilute to 200 ml. with water and shake well. This solution is referred to in the method of titration as *the conversion solution*.

METHOD OF TITRATION. Measure into a 200 ml. round-bottomed flask 5 ml. of Fehling's solution (see later), and heat over a naked flame with continuous rotation of flask until solution boils. Run from a burette into the boiling liquid 5 ml. of the conversion solution, and subsequently further quantities. After each addition boil the liquid, the flask being continuously rotated. When the blue colour of the copper solution has nearly disappeared add 0.2 ml. of 1% aqueous solution of methylene blue. Continue the titration with small quantities of the conversion solution, drop by drop, until the blue colour just disappears. (Notes.)—The indicator is not added until the end-point is nearly reached since the final change is very rapid. The complete decolorisation of the methylene blue is indicated by the whole reaction liquid, in which the precipitated cuprous oxide is continually being churned up, becoming bright red or orange in colour. To ensure that the end-point has been reached hold the flask against a sheet of white paper, and if the indicator is completely decolorised there will be no blue tint at the edge of the liquid. The boiling process must be sufficiently continuous to prevent air obtaining access to the flask and so causing oxidation of the indicator with reappearance of the blue colour.)

If the volume of the conversion solution used to reduce 5 ml. of Fehling's solution is less than 20 ml. or more than 25 ml., the conversion must be repeated using less or greater quantities of the malt extract solution, to obtain a titration between these limits. If the extract solutions become aerated or subjected to warm conditions, re-weigh and carry out the dilutions again.

A first titration to obtain approximate results is to be followed by a second, and third if necessary, to establish the end-point accurately. A confirmatory titration should be carried out in every case.

FEHLING'S SOLUTION. Measure into a dry flask equal quantities of the solutions Nos. 1 and 2, and mix.

Solution No. 1. One litre to contain 69.28 g. of crystallised copper sulphate, $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$.

Solution No. 2. One litre to contain 346 g. of Rochelle salt and 150 g. of sodium hydroxide.

Freshly mix for each day's determination.

Checked against 0.1% standard invert sugar solution by the method of titration described above, 5 ml. of Fehling's solution corresponds to 0.02533 g. of invert sugar.

Method of Calculating Diastatic Activity (Lintner Value). Express the result according to the following formulæ:—

(a) In the case of flour, diastatic activity (or Lintner value)

$$= \frac{1000}{X \times Y}$$

(b) In the case of syrup, diastatic activity (or Lintner value)

$$= \frac{1000}{X \times Y} \text{ minus } 9.$$

Where X = number of ml. of 5% malt extract solution in 100 ml. of the conversion solution.

Y = number of ml. of conversion solution required to reduce 5 ml. of Fehling's solution.

And 9 = a constant denoting the assumed equivalent of the reducing sugars present in the malt extract (syrup) used in making the determination.

(b) **FIBRE CONTENT.** Extract 2 to 3 g. with petroleum spirit, b.p., 30° to 60°, in an extraction apparatus, or at least three times by stirring, settling and decantation, and transfer the dry residue to a conical 1000 ml. flask. The material must not be further ground during extraction. A volume of 200 ml. of solution containing 1.25 g. of sulphuric acid (H_2SO_4) per 100 ml. measured at ordinary temperature and brought to boiling point is added and heated. The contents of the flask must boil within one minute and the boiling throughout must be gentle, and continuous for exactly 30 minutes, the original volume being maintained. Rotate the flask every few minutes. After 30 minutes remove the flask and pour contents into the shallow layer of hot water remaining in a funnel fitted with a pump-plate, or into the similar layer remaining in a Buchner funnel. Prepare the funnel by cutting a piece of cotton cloth or filter paper to cover the holes, so as to serve as a support for a disc of ordinary filter paper; pour boiling water into the funnel and allow to remain until funnel is hot, when suction is applied. Discard the experiment if the time of filtration of the bulk of the 200 ml. exceeds 10 minutes. Wash the residues with boiling water until the washings are free from acid. Then wash the residue from the filter paper back to the flask with a volume of 200 ml. of a solution of sodium hydroxide, containing 1.25 g. of sodium hydroxide (NaOH) per 100 ml., free from sodium carbonate, measured at ordinary temperature, and brought to boiling point. Boil the contents of the flask for exactly 30 minutes, the precautions given for the treatment with acid being observed. At the end of 30 minutes, remove the flask and filter its contents through an ordinary filter paper. Wash the residue collected in the filter paper with boiling water, then with solution of 1% hydrochloric acid and again with boiling water until free from acid. Wash the residue twice with 95% alcohol, and three times with ether. Transfer the residue to a dried weighed ashless filter paper, dried at about 100° in an oven and weighed in a weighing bottle until constant in weight. Determine the ash of the paper and contents by incineration at a dull red heat. Subtract the weight of ash from the increase of weight found on the paper and report the difference as fibre.

ASH CONTENT. Ascertain the ash content by heating a measured quantity of the substance in a muffle furnace at such a temperature that the ash does not fuse.

PROTEIN CONTENT. Ascertain the amount of soluble protein by multiplying the amount of nitrogen present (other than ammoniacal or nitric nitrogen, if any) by 6.25.

MALT EXTRACTS PRODUCED FROM BARLEY GROWN IN ENGLAND AND WALES: GRADE DESIGNATIONS AND DEFINITIONS

(S.R. and O., 1933, No. 540)

(a) *Pharmaceutical Malt Extract*

Grade Designation	Definition of Quality †
All-English (Pharmaceutical) Malt Extract or alternatively* National Mark (Pharmaceutical) Malt Extract.	<p><i>General.</i> The Extract shall be prepared from sound, clean, malted grain by digestion with water at a suitable temperature and by evaporation of the strained liquid under reduced pressure at a temperature not exceeding 55° until an amber or yellowish-brown viscous product is obtained having the characteristic agreeable odour and sweet taste. The product shall be miscible with water in all proportions, forming a translucent solution.</p> <p><i>Special.</i> The protein content shall be not less than 4.5% of the total weight. The arsenic content shall not exceed 1.4 parts per million. The sp. gr. at 15.5° shall be from 1.40 to 1.42, and the refractive index at 20° from 1.4892 to 1.4976.</p>

*The alternative "National Mark" may only be used in connection with pharmaceutical malt extract to which the grade designation mark as set out in the Fourth Schedule has been lawfully applied in accordance with the Agricultural Produce (Grading and Marking) (General) Regulations, 1928. (S.R. & O., 1928 (No. 674), p. 10).

†Extract of Malt as defined in the *British Pharmacopæia*, 1932, would conform with these requirements.

(b) *Bakers' and Veterinary Malt Extracts*

Grade Designation	Definition of Quality	
	Particular Characteristics	Common Characteristics
All-English (Bakers') Malt Extract (White Bread)	Diastatic activity shall be not less than 40 Lintner value	<i>General.</i> The product in each case shall be the water-soluble extract derived from commercially sound, clean malted grain.
All-English (Bakers') Malt Extract (Brown Bread)	None	<i>Special.</i> The specific gravity at 15.50° shall be not less than 1.4 and the soluble protein-content not less than 4.5% of the total weight.
All-English (Veterinary) Malt Extract	None	

MALT FLOURS PRODUCED FROM BARLEY AND/OR WHEAT GROWN IN ENGLAND AND WALES: GRADE DESIGNATIONS AND DEFINITIONS

Grade Designation	Special Characteristics	Common Characteristics
All-English Malt Flour (White Bread)	Diastatic activity shall be not less than 40 Lintner value	<i>General.</i> The flour shall be the pure ground product of cleaned malted grain and be sound, free from taint or objectionable flavour and of good keeping quality.
All-English Malt Flour (Brown Bread)	None	<i>Special.</i> The maximum content of water shall be 10%, of ash 1.3%, and of fibre 2.5% of the total weight.

EXTRACTUM PITUITARII

Pituitary (posterior lobe) Extract. This extract is controlled by the Therapeutic Substances Act 1925, and is official in B.P. '32 and U.S.P. X.

BIOLOGICAL METHODS OF ASSAY

Its potency can be determined by its stimulant action on the isolated uterus of the guinea-pig, which is known as its oxytocic property, by its pressor action on the blood pressure of the spinal cat, and also by its antidiuretic effect on rats. An international standard has been adopted consisting of a quantity of dry acetone-extracted posterior lobe material which is kept in the National Institute for Medical Research, Hampstead. The unit is the amount of activity present in 0.5 mg. of the standard powder.

Estimation of Oxytocic Potency. The determination of the action on the uterus is made by excising one horn of the uterus of a virgin guinea-pig and suspending it in a bath of Ringer's solution which is oxygenated and maintained at 37°. The muscle is very thin and, when pituitary extract is added to the bath, quickly responds by contraction. The extent of the contraction is proportional to the dose, hence the potency of an unknown solution can be found by comparing the contraction which a given amount of it produces with the contraction produced by a given amount of the standard extract. In practice, difficulties arise because the muscle of the horn changes in sensitiveness and wrong conclusions may easily be drawn respecting the potency of an unknown solution. The test usually takes one or two days to complete.

Estimation of Pressor Activity. The estimation is made on the blood pressure of a spinal cat, prepared as described under Adrenaline (q.v., p. 31). An intravenous injection of pituitary extract causes a rise of blood pressure not so rapid as that produced by adrenaline but lasting much longer. The height of the rise is proportional to the dose and an unknown preparation is examined to see what amount produces the same rise as that produced by a given amount of the standard extract. The test takes much time, as successive doses must be separated by an interval of one hour; this is necessary because successive injections of the same dose at shorter intervals produce a diminishing response.

Estimation of Antidiuretic Activity. A reliable method of estimating activity which is economical in skilled labour depends on the antidiuretic effect which may be observed in rats. If a group of four rats, kept without food overnight, is given water by stomach tube, in a dose of 5 ml. per 100 g. body weight, then a diuresis occurs which reaches a maximum in 60 to 90 minutes. If a dose of pituitary extract be given at the time the water is administered, the excretion of water is delayed and the maximum diuresis may not occur until 130 or 190 minutes according to the dose. To compare an unknown extract with the standard, sixteen rats receive water and eight of these are injected with standard extract and eight with the unknown extract. The time of maximum diuresis is determined for each group of eight rats. Two days later the experiment is repeated, reversing the groups, so that the eight rats which previously received the standard now receive the unknown, and *vice versa*. The antidiuretic effect of the standard and of the unknown extract is now known for all of the sixteen rats. From these measurements the potency of the unknown extract can be expressed in terms of that of the standard by using a predetermined curve relating antidiuretic effect to dose. The antidiuretic potency of different commercial extracts expressed in units is almost always the same as the oxytocic potency expressed in units. (see Burn, *Quart. J. Pharm.*, 1931, 517).

Commercial pituitary extracts supplied as containing 10 units per millilitre may vary as much as 400% in antidiuretic potency. Extracts which are to be used for their antidiuretic effect must be assayed for this activity.—F. Wokes, *Quart. J. Pharm.*, 1932, 390.

Anterior Lobe of the Pituitary Body. The anterior lobe of the pituitary body contains hormones which are partially separable and have at least four different properties, which can be estimated quantitatively with some approach to accuracy.

Gonadotropic Hormone. The injection of extracts of the anterior lobe produces various effects on the ovaries which are probably due to different factors. These effects are to cause (1) an increase in weight of the ovary; (2) an increase and enlargement of egg follicles; (3) an increased formation of oestrin as shown by the premature opening and cornification of the vagina; (4) discharge

of ova from the ovaries; and (5) the formation of corpora lutea. All these effects are ascribed to the gonadotropic hormone, but it is thought by many that the factor responsible for the stimulation of oestrin formation leading to enlargement of egg follicles and premature opening of the vagina is certainly different from the luteinising factor which produces corpora lutea and is probably responsible for ovulation.

The usual method of standardising the gonadotropic hormone, whether prepared from the anterior lobe of the pituitary or from urine of pregnancy, is to inject into infantile rats or mice, using six injections at 12-hour intervals, and then to determine whether the vagina opens and whether the canal contains the squamous cells characteristic of œstrus. A better method is that proposed by Janssen and Loeser (*Arch. exp. Path. Pharmac.*, 1930, 151, 188) in which infantile rats are injected as described and the ovaries are examined for corpora lutea. The unit is taken as that dose producing corpora lutea in ten out of twenty animals.

Recently, Hill, Parkes and White (*J. Physiol.*, 1934, 81, 335) have proposed a method of estimating the ovulation-producing substance by means of its property of causing ovulation in the œstrous rabbit. The method depends on the fact that ovulation never occurs spontaneously in the rabbit but only after copulation or after injection with the hormone. In the adult female non-pregnant rabbit carefully segregated from the male, the ovaries always contain eggs waiting to be discharged. Full-grown female rabbits (3 to 4 kg.) may be used, which, when received from the dealer, must be kept for 5 weeks in order that pregnant animals may complete pregnancy and regain the œstrous condition. The extract to be tested is then injected into a batch of twenty rabbits, the dose being administered intravenously. On the following day the ovaries are examined by making incisions into the abdominal cavity under ether anæsthesia, using full aseptic precautions. The number of animals which have ovulated is thus determined. When this number is expressed as a percentage of the number of animals injected, the amount of extract containing 1 unit, which is the amount producing a 50% response, may be calculated from a curve relating dose to percentage of animals responding, which has been determined.

Pregnancy Diagnosis. The action of the gonadotropic hormone on injection is the basis of certain tests for the diagnosis of pregnancy.

Descriptions of the Ascheim-Zondek test and the Friedman test as used at the Edinburgh Pregnancy Diagnosis Station.—J. M. Robson, *Brit. med. J.*, i/1934, 1064.

FRIEDMAN PREGNANCY TEST. Depends upon the fact that in rabbits the urine of human pregnancy produces corpora hæmorrhagica within 24 hours owing to presence of Prolan B. The active principle in the urine remains potent for at least 6 days, and a positive reaction is obtained as early as 21 days after conception.—P. M. F. Bishop, *Guy's Hosp. Rep.*, July 1933, 308, *Brit. med. J.*, ii/1933, 92.

Tests at the Edinburgh Pregnancy Diagnosis Station yield an accuracy of not less than 97%. Pregnancy can be recognised as early as 10 to 14 days after conception and reports are despatched in from 1 to 5 days according to the particular test made. All that is required as test material is 50 ml. of morning urine.—F. A. E. Crew, *Brit. med. J.*, ii/1934, 531.

Thyrotropic Hormone. This hormone produces hypertrophy of the thyroid gland, as is easily demonstrated in the guinea-pig; the change in the guinea-pig has been adapted by Rowlands and Parkes (*Biochem. J.*, 1934, 1829) as a means of estimation. Immature animals weighing 200 g. are used, in which the thyroids normally have an average weight of 31 mg. Groups of ten animals are injected daily for 5 days with the extract, and killed on the day after the last injection. The thyroids are removed, fixed in Bouin's solution, and weighed. The average weight may be 80 mg. if the extract is sufficiently potent. Since it has been shown that the increase in weight is directly proportional to the logarithm of the dose, it is possible to calculate from the observed weight of thyroids from injected animals the amount of extract which would have increased the average weight to 60 mg. This amount is defined as 1 unit.

Growth Hormone. Extracts of the anterior lobe of the pituitary body have the property of causing resumption of growth in adult animals, or in animals from which the pituitary has been removed. The extract is usually tested by injection into rats. If normal adults are used, the average weight of a group of rats is observed from day to day, and injections are given for 3 days, during which the average weight of the group is observed. Two extracts may be compared

by making simultaneous observations on two groups of rats kept under identical conditions. There is no commonly accepted unit.

Prolactin. Prolactin is the factor present in anterior lobe extracts which causes increased activity of the mammary gland, including increased secretion of milk. It may be tested by its effect on the crop glands of the pigeon. In the normal pigeon these are so small as to be identified with difficulty; after daily injection for 7 days they may reach the weight of 4 g. The amount of extract causing this increase in size is taken as 1 unit.

FERRUM

Ferri Carbonas Saccharatus (*B.P.* '32). Assayed for ferrous iron content by titration of a phosphoric acid solution, diluted with warm water and 25% *w/v* sulphuric acid, with N/10 potassium dichromate using diphenylamine as indicator. Ferrous iron content, as FeCO_3 , not less than 50%. The *U.S.P. X* preparation is made with lactose and sucrose, instead of glucose; it should contain not less than 15% of FeCO_3 ; potassium ferricyanide indicator is used in the dichromate titration. Ferrum carbonicum cum Saccharo, *P.G. VI*, contains from 9.5% to 10% of iron. Ferrum oxydatum cum Saccharo, *P.G. VI*, contains from 2.8% to 3% of iron.

The iodate method is suitable for the assay of the saccharated iron compounds of the *B.P.* and *B.P.C.* and of ferrous lactate. Ferrous iron may be titrated with accuracy by iodate in the presence of liquid glucose, acacia, tragacanth, sucrose, invert sugar in small amounts, lævulose, dextrose, lactose, glycerin, lactic acid and citric acid. Invert sugar in great excess produces a small error. The method is unsatisfactory in the presence of liquorice, marsh-mallow, quinine and aqueous extract of cochineal.—G. J. W. Ferrey, *Quart. J. Pharm.*, 1935, No. 3.

Ferri et Ammonii Citras (*B.P.* '32). Contains from 20.5% to 22.5% of Fe. The assay by warming with 30 parts of water and 2 parts of sulphuric acid, oxidising the cooled solution with N/10 potassium permanganate, allowing interaction to proceed for 3 minutes with 30 parts of hydrochloric acid and 4 parts of potassium iodide, and titrating the liberated iodine with N/10 sodium thiosulphate, replaces the *B.P.* '14 method of weighing the ignited residue. Ferri et Ammonii Citras, *U.S.P. X*, should contain from 16% to 18% of Fe, and is assayed by digestion of a solution with hydrochloric acid and potassium iodide at 40° during 30 minutes. Ferrum citricum ammoniatum, *P. Helv. V*, is assayed iodometrically and should contain from 17% to 18% of iron.

Ferri et Ammonii Citras Viridis (*B.P.C.* '34). Fe content, determined as for Ferri et Ammonii Citras, from 14% to 16%.

Ferri et Mangani Citras (*B.P.C.* '34). Assayed by the method for Ferri et Ammonii Citras, should contain not less than 14% of Fe, and not less than 7% of Mn. Estimated by the process of the *B.P.C.* '34: 0.1 g. boiled till a clear solution is produced with 25 ml. of dilute nitric acid, is heated with 12 ml. of N/10 silver nitrate and 1 g. of ammonium persulphate for 30 seconds after oxidation commences; the cooled solution is titrated with N/100 sodium arsenite to the disappearance of pink colour; each millilitre of N/100 sodium arsenite is equivalent to 0.0011 g. Mn.

In titrating potassium permanganate solution containing nitric acid with sodium arsenite, the latter has a reducing value greatly in excess of that shown when no acid is present. A manganic compound is probably formed.—*Abst. Ann. Rep. Chem. Soc.*, 1919 (Vol. XV), p. 135.

Ferri et Potassii Tartras (*B.P.C.* '34). By the assay process for Ferri et Ammonii Citras, it contains not less than 20% of Fe.

Ferri et Quininæ Citras (*B.P.* '32). Contains from 14.5% to 15.5% of anhydrous quinine and from 12% to 14% of Fe. Assayed for quinine by extraction with ether from ammoniacal solution, finally drying at 100° and weighing; the aqueous solution, warmed to expel ether and excess of ammonia, is then titrated for Fe content as for Ferri et Ammonii Citras.

Ferri et Strychninæ Citras (*B.P.C.* '34). By extraction with chloroform from ammoniacal solution, drying at 100° and weighing, a strychnine content of from 0.95% to 1.05% should be indicated; titration of the aqueous liquids from this assay should indicate from 12% to 14% of Fe.

Ferri, Quininæ et Strychninæ Citras (*B.P.C.* '34). Contains 14.5% to 15.5% of anhydrous quinine, 0.95% to 1.05% of strychnine, and 12% to 14% of Fe. Assayed by extraction of the total alkaloids with chloroform from ammoniacal solution, drying at 100° and weighing; the strychnine is separated by the *B.P.* '32 process for Syrupus Ferri Phosphatis cum Quinina et Strychnina (given below), and subtracted from the total alkaloids to give quinine content; the aqueous liquids from the total alkaloids extraction are titrated for Fe as for Ferri et Ammonii Citras.

Ferri Perchloridum (*B.P.C.* '34). $\text{FeCl}_3 \cdot 6\text{H}_2\text{O} = 270.3$. By precipitation as hydroxide and ignition, a residue of Fe_2O_3 equivalent to from 57% to 63% of FeCl_3 should be obtained. Ferri Chloridum, *U.S.P. X*, is assayed by titration of the iodine, liberated from potassium iodide in acid solution, with N/10 sodium thiosulphate, and should correspond to not less than 20% of Fe.

Liquor Ferri Perchloridi (*B.P.* '32). Yields Fe_2O_3 equivalent to from 14.25% to 15.75% *w/v* of FeCl_3 . Liquor Ferri Chloridi, *U.S.P. X*, estimated by the potassium iodide method, contains ferric chloride equivalent to from 10% to 11% of Fe. Liquor Ferri sesquichlorati, *P.G. VI*, contains from 9.8% to 10.3% of iron.

Liquor Ferri Perchloridi Fortis (*B.P.C.* '34). Should contain from 58.5% to 61.5% *w/v* of FeCl_3 , corresponding to about 20% of Fe. Sp. gr., about 1.43. Lead limit, 50 parts per million.

Ferri Phosphas (*B.P.C.* '34). By the *B.P.* potassium dichromate method used for Ferri Carbonas Saccharatus, it contains not less than 47% of ferrous salts, calculated as ferrous phosphate, $\text{Fe}_3(\text{PO}_4)_2 \cdot 8\text{H}_2\text{O}$.

Ferri Phosphas Saccharatus (*B.P.C.* '34). Contains not less than 60% of ferrous salts, calculated as $\text{Fe}_3(\text{PO}_4)_2 \cdot 8\text{H}_2\text{O}$ and assayed by the *B.P.* method for Ferri Carbonas Saccharatus.

Syrupus Ferri Phosphatis (*B.P.C.* '34). By the *B.P.* titanous chloride titration method used for Syrupus Ferri Phosphatis Compositus, an iron content equivalent to from 1.7% to 1.9% *w/v* of $\text{Fe}_3(\text{PO}_4)_2$ should be indicated.

Syrupus Ferri Phosphatis Compositus (*B.P.* '32). Contains iron equivalent to from 0.85% to 0.95% *w/v* of anhydrous ferrous phosphate, $\text{Fe}_3(\text{PO}_4)_2$, and calcium equivalent to from 1.3% to 1.5% *w/v* of tricalcium phosphate. Assayed for iron by diluting a weighed portion with water, adding a few drops of hydrochloric acid and a 2% potassium permanganate solution until a transient pink colour is produced throughout the solution; after addition of more hydrochloric acid and sodium bicarbonate, N/10 titanous chloride solution is added until the commencement of the titration is indicated by the production of a blue colour on adding one drop of the titration liquid to one drop of potassium ferricyanide solution; the ferric iron is then titrated with N/10 titanous chloride using ammonium thiocyanate solution as indicator. Calcium is determined by well diluting a weighed portion, adding citric acid, and boiling, making just alkaline with ammonia, then adding acetic acid and, to the boiling solution, excess of ammonium oxalate solution; after boiling gently on a sand-bath for 2 hours, the precipitate is collected, washed and ignited with sulphuric acid.

Syrupus Ferri Phosphatis cum Quinina et Strychnina (*B.P.* '32). Should contain iron equivalent to from 1.62% to 1.98% *w/v* of $\text{Fe}_3(\text{PO}_4)_2$, 1.04% to 1.2% *w/v* of anhydrous quinine, and 0.022% to 0.027% *w/v* of strychnine. Assayed for iron by the titanous chloride titration method; for quinine, by adding sodium citrate to a dilution of the syrup and sodium hydroxide solution and extracting with chloroform; from the weight of the dried residue of total alkaloid the weight of strychnine is subtracted; the residue of total alkaloid is then dissolved in N/1 hydrochloric acid and an equal volume of saturated sodium chloride solution and extracted five times with 5-minute shakings with chloroform; the chloroform liquids are shaken with water and ammonia solution, evaporated, alcohol added, evaporated and dried at 100° ; the residue is then washed with three 2 ml. portions of (2 : 1) ether and light petroleum (b.p. 50° to 60°) saturated with strychnine, evaporated with alcohol and, after drying at 100° , the residue of strychnine is weighed.

Ferri Sulphas (*B.P.* '32). $\text{FeSO}_4 \cdot 7\text{H}_2\text{O} = 278.0$. By titration with N/10 potassium permanganate, it should contain not less than 99% of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$.

the *U.S.P. X* salt contains from 54·36% to 57·07% of anhydrous ferrous sulphate, corresponding to about 99·5% of the heptahydrate.

Ferri Sulphas Exsiccatus (*B.P. '32*). Contains not less than 80% of FeSO_4 . The *U.S.P. X* substance is of the same strength.

Ferrum (*B.P. '32*). The fine bright wire should have a diameter of about 1 mm. (No. 42 standard wire gauge) and contain not more than 200 parts of arsenic per million. Much of the wire on the market contains more arsenic than the *B.P.* allows. The *U.S.P. X* includes no standard.

Iron wire, No. 42 S.W.G., as specified in the *B.P.*, is not a commercial article. The *B.P. '14* required simply "No. 35 wire gauge" and No. 35 S.W.G., with a diameter of 0·0084 in. or 0·2134 mm., was usually supplied.—*Pharm. J.*, 1933, 698.

Ferrum Redactum (*B.P. '32*). Contains not less than 80% of metallic iron. Assayed by interaction with a hot copper sulphate solution and titration of the filtered and acidified liquid with N/10 potassium permanganate. Ferrum reductum, *U.S.P. X*, should contain not less than 90% of metallic iron; interaction at boiling-point with corrosive mercuric chloride is used for assaying, followed by adjustment to volume and titration of an aliquot part of the filtered liquid with N/10 potassium permanganate.

Ferrum pulveratum, *P.G. VI*, contains not less than 97·6% of iron, and Ferrum redactum, *P.G. VI*, should contain not less than 96·5% of iron or not less than 90% of metallic iron. Ferrum reductum, *P. Helv. V*, contains not less than 90% of metallic iron; it is assayed by interaction with a boiling solution of mercuric chloride and titration of the filtrate with potassium permanganate solution.

The Assay of Reduced Iron. The copper sulphate method for the determination of metallic iron in reduced iron has been shown to yield inaccurate and variable results. The modification of the Wilner-Merck process suggested yields consistent results which reflect the actual content of metallic iron in the sample. The method recommended is as follows:—To approximately 0·5 g. of sample in a clean, dry 100 ml. graduated flask add 2·5 g. of mercuric chloride (sulphide-free) and about 50 ml. of recently boiled and cooled distilled water. Boil gently for 20 minutes (avoiding excessive frothing) with frequent shaking, make the volume up to 100 ml. with recently boiled and cooled distilled water, cork the flask and cool. When cold, adjust the volume to 100 ml., shake well, allow the precipitate to settle, filter rapidly into a clean, dry conical flask, pipette 50 ml. of the filtrate into 100 ml. of dilute sulphuric acid in which 2 g. of manganese sulphate has been dissolved, and titrate with N/10 potassium permanganate solution.—Hartley, Linnell, Read and Rolfe, *Quart. J. Pharm.*, 1935, 100.

Iron Content of Foods. Of 150 common food materials examined the figures for iron content ranged from 0·00015% for lemon juice to 0·0192% for parsley. Arranged in descending order—dried legumes, green leafy vegetables, dried fruit, nuts, cereals, poultry, green legumes, roots and tubers, non-leafy vegetables, fish and fruits. Cabbages, celery and head lettuce are low in iron; salt-water fish contain more iron than fresh-water fish, and fish with dark-coloured tissue more than those with light-coloured, and the dark meat of poultry more than the light meat.—*J. Amer. med. Ass.*, ii/1928, 251.

Determination of Traces of Lead and Copper in Medicinal Iron Preparations. To 2 g. of sample in a 350 ml. hard glass flask add 5 ml. of water and 10 ml. of sulphuric acid. Heat gently, add slowly 10 ml. of 30% hydrogen peroxide (100 vols.), and boil. Add more hydrogen peroxide as necessary to oxidise the organic matter completely, as indicated by the absence of charring when all the excess water has been boiled off. Cool, add 50 ml. of water and 10 ml. of hydrochloric acid, and boil until a clear solution is obtained. Cool and add a solution of 10 g. of citric acid in 50 ml. of water and 50 ml. of strong solution of ammonia. Cool and neutralise to litmus paper with dilute solution of ammonia, adding a further 10 ml. of the dilute ammonia solution. Transfer to a separator and extract three times with 10 to 15 ml. portions of a 0·1% *w/v* solution of diphenylthiocarbazone in chloroform. Each extract is washed in a second separator with about 20 ml. of water, transferred to a small flask and the chloroform evaporated. Add 0·5 ml. of sulphuric acid to the residue and destroy organic matter by heating with a few drops of nitric acid, then remove nitric acid by adding a few drops of water to the cooled solution and heating until white fumes appear. The solution contains all the Cu and Pb. Dilute with water, add 1 g. of citric acid and 4 g. of ammonium acetate, and, when solution is complete, make slightly alkaline with ammonia and dilute with water to 100 ml. To determine the Cu, transfer

25 ml. to a Nessler glass, neutralise to litmus with glacial acetic acid, add 2 ml. in excess, dilute to 100 ml. with water and add 1 ml. of a 0.1% *w/v* solution of dithio-oxamide in alcohol (95%). Compare the colour produced with that obtained with a solution containing 1 g. of ammonium acetate and a suitable quantity of standard copper sulphate solution containing 0.00001 g. of Cu per millilitre. The amount of copper solution used should not exceed 6 ml. otherwise a smaller amount of the original solution must be used. The Pb is determined by transferring 25 ml. of the original solution to a Nessler glass, adding 1 ml. 10% *w/v* KCN solution and a little dilute ammonia, diluting to 50 ml. with water, adding 0.1 ml. of 10% sodium sulphide solution and matching in the ordinary way against the *B.P.* dilute solution of lead PbT, using an auxiliary solution containing 1 g. of ammonium acetate, 1 ml. of 10% *w/v* potassium cyanide solution and the same amount of Cu as is known to be contained in the primary solution. The amount of standard lead solution used must not exceed 10 ml.—N. L. Allport and G. H. Skrimshire, *Quart. J. Pharm.*, 1932, 460.

Traces of lead may be separated from considerable quantities of iron by extracting the iron, as ferric chloride, with ether from solution in 25% to 27% *w/v* hydrochloric acid.—A. D. Powell and G. F. Hall, *Quart. J. Pharm.*, 1932, 45.

Minute amounts of copper in the presence of iron and certain other metals can be determined colorimetrically by means of diethyldithiocarbamate after extraction with carbon tetrachloride.—L. A. Haddock and Norman Evered, *Analyst*, 1932, 495.

FILIX MAS

Filix Mas (*B.P.* '32). Contains not more than 2% of other organic matter. Crystals of calcium oxalate should be absent, and it should yield not more than 6% of ash and 2% of acid-insoluble ash. *Aspidium*, *U.S.P. X*, should yield not less than 65% of greenish oleoresin, prepared as *Oleoresina Aspidii* by evaporation of the ether percolate. *Rhizoma Filicis*, *P. Helv. V*, contains not less than 1.8% of crude filicin when determined by applying the usual baryta process to the residue obtained after percolation of the drug with ether.

Extractum Filicis (*B.P.* '32). Contains from 24% to 26% *w/w* of filicin. Sp. gr., not less than 1.000. n_{D40° , not less than 1.492. Determined by the *B.P.* method by shaking 5 g. in 40 ml. of ether with 100 ml. of barium hydroxide solution; 87 ml. of the separated filtered aqueous liquid (=4 g. of extract) acidified with hydrochloric acid, and extracted with 30, 20 and 15 ml. portions of ether; the filtered and evaporated ether extracts are dried at 100° and weighed as filicin. *Oleoresina Aspidii*, *U.S.P. X*, yields not less than 24% of crude filicin. Sp. gr., not less than 1.00 at 25°. *Extractum Filicis*, *P.G. VI*, should contain not less than 25% of crude filicin.

Assay of male fern by estimating the phloroglucides with silver.—*Pharm. J.* i/1930, 321.

FŒNICULUM

Fœniculum (*B.P.* '32). Contains not more than 2% of other organic matter and yields not more than 12% of ash. The *N.F.* allows a limit of 4% of foreign organic matter for *Fœniculum*. *Fructus Fœniculi*, *P.G. VI*, is required to yield not less than 45% of volatile oil.

The Food and Drug Administration of the U.S. Dept. of Agriculture defines fennel seed as the dried fruit of cultivated varieties of *Fœniculum vulgare* Hill. Contains not more than 9% of total ash, and not more than 2% of ash insoluble in hydrochloric acid.—*S.R.A., F.D. No. 2, Rev. 4*, Aug. 1933.

Oleum Fœniculi (*B.P.C.* '34). Using a crystal of congealed oil of anise to induce crystallisation, the f.p. (by the *B.P.* method employed for *Oleum Anisi*) is not below 3°. Sp. gr., 0.960 to 1.000. α_D , +4° to +24°. n_{D20° , 1.525

550. The *U.S.P. X* uses a small crystal of the substance being tested in determining the f.p. of *Oleum Fœniculi*, which should not fall below 3° . Sp. gr., 0.953 to 0.973 at 25° . $n_{D20^{\circ}}$, 1.5280 to 1.5380. α_D at 25° , $+12^{\circ}$ to $+24^{\circ}$.

GELATINUM

Gelatinum (*B.P. '32*). A 2% *w/v* hot aqueous solution is colourless and sets to a transparent or translucent jelly on cooling. Sulphur dioxide limit, 1000 parts per million. Ash, not more than 2%. The *U.S.P. X* sulphur dioxide limit for Gelatinum is 0.004%, by distillation with phosphoric acid into N/10 iodine and precipitation with barium chloride.

GELSEMIUM

Gelsemium (*B.P.C. '34*). Contains not more than 2% of foreign organic matter. The *N.F. V* allows the same limit.

A standard of 0.5% total alkaloids for the root, and 0.05% for the tincture has been suggested.

For a lengthy account of the work of L. E. Sayre, C. W. Moore and others (1911) on the gelsemium alkaloids, also the suggestion to use the name *sempervirine* to replace the amorphous gelsemine, see *Edn. XVIII*, Vol. II, p. 74, 75, and *Yearb. Pharm.*, 1920, 10.

Identification of Gelsemium. It does not contain aesculin. The fluorescent body is scopoletin (aesculetin-5-methyl ether). If 0.5 g. of the ground drug be heated in a tube with chloroform, the mixture filtered and the filtrate shaken with water to which a few drops of dilute ammonia have been added, the aqueous layer on separation shows a distinct blue fluorescence, indicating presence of scopoletin.—F. Tutin, *Pharm. J.*, i/1912, 157.

GENTIANA

Gentiana (*B.P. '32*). Contains not more than 2% of foreign organic matter. Water-soluble extractive, not less than 33%. Ash, not more than 6%. Gentiana, *U.S.P. X*, should yield not less than 30% of water-soluble extractive.

Calumba (*B.P. '32*). Foreign organic matter, not more than 2%. Ash, not more than 9%. Calumba, *U.S.P. X*, should yield not more than 2.5% of acid-insoluble ash.

The *B.P.* standard for other organic matter is too low.—*Pharm. J.*, ii/1932, 68.

GLYCERINUM

Glycerinum (*B.P. '32*). $C_3H_8O_3 = 92.06$. Sp. gr., 1.260 to 1.265 (corresponding to from 98% to 100% of $C_3H_8O_3$). $n_{D20^{\circ}}$, 1.470 to 1.473. Ash, not more than 0.01%. Glycerinum, *U.S.P. X*, contains not less than 95% of $C_3H_8O_3$; sp. gr. at 25° , not below 1.249.

Glycerinum, *P.G. VI*, contains from 84% to 87% of anhydrous glycerin; sp. gr., 1.221 to 1.231. Glycerinum, *P. Helv. V*, has a sp. gr. of 1.224 to 1.234 and contains from 84% to 88% of $C_3H_5(OH)_3$, whilst Glycerinum concentratum has a sp. gr. of 1.260 to 1.266 and contains at least 98% of $C_3H_5(OH)_3$.

Ethylene Glycol : Detection in the Presence of Glycerin. To 10 ml. of test sample add 2 ml. of nitric acid and evaporate to 1 ml., then add 5 ml. of 20% *w/v* ammonium chloride and allow to cool. Make alkaline by adding, 1 ml. at a

time, 10% sodium hydroxide until there is a slight smell of ammonia. Boil off the free ammonia and add 1 ml. of 10% *w/v* barium chloride. After cooling the mixture for about 15 minutes, filter and wash with about 5 ml. of water. Rinse the precipitate into a boiling tube with 5 ml. of water, add 7.5 ml. of 2N sulphuric acid and heat to boiling. Cool and filter. The filtrate is treated with 0.6 N permanganate until no more is decolorised in the cold and is then boiled. Any further decolorisation shows the presence of oxalic acid, that is of glycol in the original product. The test will detect 1% of glycol in water or 3% in a mixture of 70% of glycerin and 27% of water.—A. W. Middleton, *Analyst*, 1934, 522.

Microscopic Glycerin Jelly. Dissolve gelatin 12.5 in water 100, add glycerin 100 (warmed), clarify with egg albumen 12.5 and to the product add salicylic acid 1 in alcohol 12.5.

Detection of Glycerin. By oxidation with permanganate and treatment with Schiff's reagent, glycerin gives a positive coloration in 0.04% solution. The common organic acids do not interfere.—*J. chem. Soc., Abstr.*, ii/1925, 162. See also *Analyst*, 1926, 382.

The identification of glycerin by a bacterial method.—A. Castellani and F. I. Taylor, *J. trop. Med. (Hyg.)*, Oct. 15, 1924, 271.

SOLUBILITIES of various chemicals in glycerin.—K. Holm, *Yearb. Pharm.* 1922, 286.

Liquor Glycerylis Trinitratis (*B.P.* '32). Determined by digesting in a closed tube with one-tenth its volume of sodium hydroxide solution for one hour, transferring with alcohol to a brine-charged nitrometer and shaking with equal volumes of potassium iodide solution and dilute sulphuric acid; each millilitre of nitric oxide produced at 15.5° and normal pressure is equivalent to 0.00505 g. of $C_3H_5O_9N_3$; from 0.9% to 1.1% *w/v* should be indicated. Alcohol content 88% to 90% *v/v* of ethyl alcohol. Spiritus Glycerylis Nitratis, *U.S.P.* 2 contains from 1% to 1.1% of $C_3H_5(NO_3)_3$, determined by allowing to evaporate spontaneously, and drying the residue over sulphuric acid.

An official quantitative method for the determination of glyceryl trinitrate (nitroglycerin) is described in Methods of Analysis (*A.O.A.C.*, 1930, 459).

Determination in Tablets. One tablet reputed to contain 1/100 gr. is crushed finely and macerated in 2.5 ml. of glacial acetic acid for 2 hours. 1 ml. of the filtered liquid is transferred to a suitable 10 ml. tube and, with the tube immersed in cold water, 0.25 ml. of a 0.5% solution of diphenylamine in nitrogen-free sulphuric acid is added. The tube is agitated in the cold water and after 3 minutes diluted to the 10 ml. mark with glacial acetic acid. The depth of colour is then compared with that given by similarly and simultaneously treating 2.4 ml. of standard solutions of KNO_3 in glacial acetic acid. For 1/100 gr., 1/150 gr. and 1/200 gr. trinitrin, standard solutions of KNO_3 should contain per 100 ml. of glacial acetic acid 0.0340 g., 0.0231 g. and 0.0173 g. respectively. C. H. Sykes, *Pharm. J.*, ii/1933, 267.

In tablets or solution, nitroglycerin can be determined by reduction with Devarda alloy and distillation of the ammonia in standard sulphuric acid. A quantity of the preparation representing about 0.05 g. of nitroglycerin is mixed in an 800 ml. Kjeldahl flask with 50 ml. of a saturated sodium sulphate solution, 150 ml. of water and sufficient 10% sulphuric acid to make the mixture acid to litmus. The mixture is distilled into a flask containing 30 ml. of 5% sodium hydroxide solution and reduction effected by means of 2 g. of Devarda alloy. E. L. Anderson, *J. Ass. off. agric. Chem., Wash.*, 1932, 140.

IMPROVED METHOD FOR TABLETS. Place five tablets in a 500 ml. Kjeldahl flask, add 25 ml. of saturated sodium sulphate solution, 75 ml. of water and sufficient sulphuric acid to make just acid to litmus paper (usually 0.3 ml. of N/1 sulphuric acid is required). Distil just to dryness, using a still head, into a flask containing 10 ml. of N/10 sodium hydroxide, keeping the outlet tube below the surface of the alkali. Wash down the condenser and outlet tube and evaporate the sodium hydroxide solution to dryness. Add 2 ml. of water, 0.3 g. (± 0.01 g.) of reduced iron and 2 ml. of 50% *v/v* sulphuric acid, allow to stand for 5 minutes and boil for 2 minutes. Transfer the acid solution to a steam distillation apparatus, make alkaline with 4 ml. of saturated sodium hydroxide solution, and distil the liberated ammonia into a flask containing 10 ml. of N/10 sulphuric acid until the distillate measures 500 ml. Take 100 ml. of the distillate, add 2 ml. of Nessler's reagent and compare the colour produced with that produced by adding the same amounts of reagent to 100 ml. of a solution containing ammonium chloride equivalent to 0.1 mg. of nitrogen.

The colours produced are most easily compared in a colorimeter, but a photometer or even Nessler glasses could be used for the purpose. Whatever means of comparing the colours is used the colour of the unknown should not vary more than 20% from that of the standard. A control experiment must always be carried out exactly as described.—Wilfred Smith, *Quart. J. Pharm.* 1935, No. 3.

Nitroglycerin is rapidly decomposed in the body and is unlikely to be found in the liver or in the urine. It might be extracted with ether from stomach contents.—*Pharm. J.*, i/1926, 406.

Erythritylis Tetranitras Dilutus (*B.P.* '32). Contains from 47.5% to 52.5% of $C_4H_6O_{12}N_4$. Estimated by the Kjeldahl method, using salicylic acid with the sulphuric acid for digestion; a blank estimation is performed using half the weight of lactose; each millilitre of N/10 sulphuric acid is equivalent to 0.007552 g. of $C_4H_6O_{12}N_4$.

GLYCYRRHIZA

Glycyrrhiza (*B.P.* '32). Water-soluble extractive, not less than 20%. Ash limits: peeled drug, not more than 6%; unpeeled drug, not more than 10%. Acid-insoluble ash, not more than 2.5%. Powdered liquorice *B.P.* is the powder of the peeled drug; a powder of the unpeeled drug is not used except when expressly named. Glycyrrhiza, *U.S.P. X*, yields not more than 2.5% of acid-insoluble ash.

The name "**glycyrrhizin**" applies to the sweet substance found in liquorice root, a mixture of calcium and potassium glycyrrhizines.

Tschirch discovered that glycyrrhizinic acid is the diglycuronic acid ester of glycyrrhetic acid. It has glycosidal properties. Glycuronic acid is of importance in animal life—an unexpected fact, since the most varied sugars are at the disposal of a plant if it wishes to form glycosides.

A minimum of 9% of "glycyrrhizin" should be present in normally prepared edible juices—they should not contain more than 18% of sugars, reducing and non-reducing. In order to determine whether the starch be actual or added, the sample should be powdered, extracted with water and the residue taken up with 3% ammonia solution. The insoluble matter should never exceed 6%. Examine this under the microscope to trace source of starch, i.e., whether added or of the same character as that in the root. The amount not dissolved in 70% alcohol should not exceed 16.5%. Gum should never be present in pure liquorice juice.—Parry, *Chem. & Drugg.*, i/1911, 133.

Glycyrrhizin—possible fatal dose 22 g., i.e., 0.45 to 0.5 g. for a dog and 1.0 g. for a rabbit per kilo.—*Pharm. J.*, i/1928, 559.

GOSSYPIUM

Gossypium Absorbens (*B.P.C.* '34). Absorbent cotton wool. A thin layer, equivalent to about 0.5 g. for an area of 70 sq. in., when viewed between glass plates, by transmitted light, is not more neppy than the standard sample kept at the Manchester Testing House. 1 g. compressed to about 20 ml. and placed lightly on water at 20° sinks or becomes saturated within 10 seconds. Average length of staple, not less than $\frac{5}{8}$ inch. Water-soluble extractive, not more than 0.5%. Ash, not more than 0.5%.

The greasy material on absorbent cotton wool consists mainly of fatty acids with a fairly large proportion of unsaponifiable matter. In commercial samples this substance is present in sufficient quantity to cover the fibres with a film of molecular thickness and the absorbency will be greater or less according to whether the fatty acids are oriented with the carboxyl groups outwards or inwards. In the latter case wetting is due to rupture of the film consequent upon the swelling of the fibres under the influence of water vapour diffusing through

the grease, and is a slower process. The orientation of carboxyl groups in the grease can be affected by external conditions, but samples impregnated with purely paraffinoid substances show only the second type of wetting.—R. Maxwell Savage. *J. Soc. chem. Ind., Lond.*, 1934, 379.

Cellulosum Ligni (*B.P.C.* '34). Cellulose wadding. Superficial area, not less than 1500 sq. in. per pound. Moisture limit, 10%. Ash limit, 0.5%. Chloroform extractive, not more than 1%. 1.5 g. compressed to about 20 ml. and placed on water at 20° sinks or becomes saturated within 5 seconds.

Linteum Absorbens (*B.P.C.* '34). Absorbent lint. Water-soluble extractive, not more than 0.5%. Superficial area, 230 to 250 sq. in. per ounce. Minimum average number of threads per inch, 39 in the warp and 24 in the weft. A piece, 3×3 in., placed, unraised side downwards, on water at 20° becomes saturated in 10 seconds.

Carbasus Absorbens (*B.P.C.* '34). Absorbent gauze. Water-soluble extractive, not more than 0.5%. Weight per sq. yd., not less than 180 gr. Average number of threads per inch, not less than 19 in the warp and 15 in the weft. A test for absorbency is included.

Tela Carbasi et Gossypii (*B.P.C.* '34). Gauze and cotton tissue. Superficial area, not less than 1800 sq. in. per pound. The absorbent gauze and absorbent cotton wool comply with the standards for *Carbasus Absorbens* and *Gossypium Absorbens* respectively.

Tela Carbasi et Gossypii Capsici (*B.P.C.* '34). Capsicum tissue. The absorbent gauze should comply with the standard for *Carbasus Absorbens*, with the exception of the colour and the weft, which has not less than 12 threads per inch. Superficial area, not less than 1800 sq. in. per pound.

Tela Carbasi et Ligni (*B.P.C.* '34). Cellulose tissue. The absorbent gauze should comply with the standard for *Carbasus Absorbens*, with the exception that the weft has not fewer than 12 threads per inch. The cellulose wadding complies with the *B.P.C.* *Cellulosum Ligni* standard. Superficial area, not less than 1350 sq. in. per pound.

ARTIFICIAL SILK

Manufacture. The first process involves the separation of cellulose from other constituents of wood pulp or cotton by boiling in 5% caustic soda, washing with water, straining and bleaching with sodium hypochlorite, again washing, drying, and cutting into suitable sheets.

There are four methods of commercial importance by which the dried pulp sheets are treated:—

- (1) **NITRO-CELLULOSE** (Chardonnet or Swan Artificial Silk), made by dissolving the cotton linters in a mixture of nitric and sulphuric acids, pressing off, washing, and partially drying. The nitro-cellulose is then dissolved in an alcohol-ether mixture, filtered and stored for use.
- (2) **CUPRAMMONIUM** (Despeissis or Pauly Artificial Silk). The purified cotton is here dissolved in Schweitzer's reagent and allowed to ripen at a low temperature for several days.
- (3) **VISCOSE ARTIFICIAL SILK** (Cross, Bevan and Beadle). This is generally xanthate of cellulose. This constitutes the greater percentage of artificial silk, and is prepared by impregnating purified wood pulp with caustic soda solution. The excess is removed and the alkali-cellulose treated with carbon disulphide. After 3 to 5 hours, the product is dissolved in water and weak caustic soda solution and agitated in a mixer until homogeneous. This is termed xanthation and the product named Viscose. After repeated filtrations the viscose in large vertical containers is then allowed to ripen. In the spinning, the viscous solution is forced through fine jets and coagulated in acid, fine filaments resulting.

Cross, Bevan and Beadle's Patent is 8700/92. The patent was prolonged for 5 years.—S. W. Woolley, *Enemy Patents and Trade Marks*, Oct. 24, 1918.

- (4) **CELLULOSE ACETATE**, "CELANESE." The purified raw material (almost invariably cotton) is here acetylated by acetic anhydride in the presence of a catalyst, usually sulphuric acid. The cellulose acetate formed is precipitated with water, and the substance then dissolved in acetone, or in a mixture of organic solvents. The product is filtered and stored. (Coagulation in this case is effected by evaporation of the solvent in warm air.)

In each instance the thick solution is drawn out into thin threads by forcing through fine jets or multiple-spinning nozzles, the orifices of which are

considerably less than 0.1 mm.—*Artificial Silk, its Manufacture and Uses*, T. Woodhouse, 1927. See also *U.S.D.*, p. 533.

Genuine silk contains 17% nitrogen, whilst artificial silk derived from cellulose contains only 0.05% to 0.13%. That obtained from proteids, e.g., casein, gelatin, etc., contains more.—Thorpe, Vol. IV, 686.

Tests for Silk. One of the simplest tests is to apply a match—pure silk is distinctly difficult to set alight and leaves a relatively large carbon ash, whilst artificial silks catch fire easily and leave little ash. *Mixtures* of artificial and natural silk with wool and cotton, are used. A mixture of artificial and real silk responds according to the proportions present. Those in the trade can tell almost by touch and by the flame test the composition of a material. It is customary in some cases to “load” the materials with chemicals, e.g., tin, to make them weigh to the touch like real silk.

Silk is soluble in Richardson’s solution (warm), concentrated aqueous zinc chloride, and in Elsner’s reagent. It is also soluble in boiling 5% sodium hydroxide solution.

RICHARDSON’S SOLUTION. Nickel sulphate 25 g. is dissolved in water and precipitated with a slight excess of sodium hydroxide. The precipitated nickel hydroxide is filtered off, washed thoroughly, dissolved in 125 ml. strong ammonia solution and diluted to 250 ml.

ELSNER’S REAGENT. Dissolve zinc chloride 100 g. in water 85 ml. and add zinc oxide 4 g. Boiling, this will dissolve silk, but not cotton or wool. Chlorine will decompose silk, and, when wet, ozone will attack it.

The quantitative determination of cotton, wool, silk and artificial silks in mixed textiles after washing and microscopical examination is described, and a table is given showing the corrections to be made with each treatment.—P. Kraus and H. Markert, *J. Text. Inst., Manchr.*, 1932, 23, 213.

Tests to Distinguish the Varieties of Artificial Silk.

The tests apply essentially to the untreated rayon. Great care must be exercised in interpreting reactions obtained with dyed fabrics, since the presence of aniline colours, mordants, and other fibres, such as cotton or real silk, may give anomalous results.

Tests	Cellulose Acetate Silk	Nitro-Cellulose Silk	Viscose Silk	Cuprammonium Silk
Solution in boiling 5% caustic soda	insoluble	almost insoluble	insoluble	insoluble
Solution in glacial acetic acid	soluble	insoluble	insoluble	insoluble
Solution in acetone	soluble	insoluble	insoluble	insoluble
Diphenylamine in conc. H_2SO_4	no blue colour	blue colour	no blue colour	no blue colour
Schweitzer’s reagent	almost insoluble	almost insoluble	readily soluble	readily soluble
Cover with conc. sulphuric acid, observe: (a) At once (b) After one hour	yellow pale brown	colourless pale yellow	reddish-brown dark brown	yellow brown
Soak in an aqueous solution of ruthenium red (1:1000 for 12 hours) and then wash.	remains undyed	dyed deep magenta	dyed a pale magenta colour	coloured irregularly pale pink and blue tints.

By carrying out the tests in the order given it is possible by a process of elimination to identify an undyed artificial silk fibre. The insolubility in 5% caustic soda distinguishes from real silk.

As confirmation for **real silk**—

Acidify a solution of sodium nitrite with hydrochloric acid, producing nitrous acid, and soak the sample for some hours in the dilute solution, then rinse well and put into a solution of β -naphthol in dilute sodium hydroxide. True silk gradually becomes maroon in colour and artificial silk remains undyed. This may be of value in mixtures of silk and artificial silk.

Cellulose Acetate and Cellulose Nitrate Solvents.

The principal solvents for cellulose acetate are acetone, methyl and ethyl formates, methyl acetate, aniline, the phenols, pyridine, quinoline, cyclohexane, methylethylketone, acetaldehyde, benzaldehyde, nitromethane, glycerin esters, mono-, di-, and tri-chlorhydrins, glycol, diacetin, benzyl acetate, furfural. It is insoluble in methyl, ethyl, butyl and isopropyl alcohols, and in carbon tetrachloride.

The solubility in tetrachlorethane is approximately 1.5%, but the addition of solvents such as benzyl alcohol, methyl alcohol, etc., gives solutions which contain up to 5% of the cellulose acetate and yield an elastic film on evaporation. Such solvents are termed **plasticisers and softeners**.

Many of these cellulose paints and varnishes are now made and applied to the surfaces *hot* by means of sprays. It is necessary to use a volatile solvent for solution, with a very small percentage of a high-boiling plasticiser added. A list of these plasticisers was published in the *Chemical Trade Journal* and *Chemical Engineer* of March 11th, 1927. Plasticisers between the b.p. range 160° to 250° should be avoided, and an even wider range might be adopted.

Amyl Phthalate. This seems to be one of the most satisfactory plasticisers. It is a good solvent for nitrocellulose, resins and "ester gum." The amount added varies from 10% to 100% of the nitrocellulose employed, with the addition of from 3% to 5% of ester gum. Hard resins up to 15% might be added with advantage. This gives a stable, weather-proof, elastic film.

Benzyl Alcohol. This is used as a softener. It causes the cellulose acetate or nitrocellulose to swell and soften into a jelly which then readily dissolves in the commoner solvents. This is used in many of the so-called stove enamels. It should be used in conjunction with a high-boiling plasticiser and a low-boiling solvent. It prevents cracking of the film. The solubility of cellulose acetate in benzyl alcohol alone in the cold is only 1%.

Tricresyl Phosphate. This is probably the best of all plasticisers. It reduces inflammability and, in conjunction with ester gum produces a film of high brilliancy and elasticity. Its advantages are its great permanency and its capability of giving a highly-polished surface.

Camphor is not now generally used. It is not a satisfactory plasticiser, since it readily volatilises and leaves a brittle film which tends to shrink.

Castor Oil can only be used in very small proportions, since it tends to produce a sticky non-drying film. It is a non-solvent for nitrocellulose and cellulose acetate.

Tetrachlorethane. A good solvent, used considerably in the cellulose paint and lacquer industry. A solution of cellulose acetate 5 g., methyl alcohol (good quality) 5 g., in tetrachlorethane 100 g., gives a film which is bright, clear and flexible. The solution evaporates in one hour. A film can be obtained from a 2% solution of cellulose acetate, with 5% benzyl alcohol in tetrachlorethane but owing to the dilution of the solution the film is weak and thin.

Ethyl Acetate. Not a good solvent for cellulose acetate, but it dissolves nitrocellulose more readily. The addition of 3% ester gum to a solution of 5% nitrocellulose in ethyl acetate gives a film which is hard and bright, but has a somewhat crinkled appearance. A mixture of ethyl acetate with 4% or 5% ethyl alcohol gives a better solvent for the acetate. Also equal parts methyl or ethyl alcohol with benzene (this is only satisfactory when warm).

A mixture of trichlorethylene and methyl alcohol equal parts has a remarkable swelling effect upon cellulose acetate, whilst the addition of a small quantity of any other solvent causes complete solution.

Inflammability Experiments. Additions of 5% and 10% hexachlorethane to benzene or amyl alcohol, do not affect the inflammability. Either solvent readily burns, whilst the benzene mixture is ignited by a spark. A cellulose enamel on the market has as solvents benzene and amyl acetate. It yields a residue of 25% which burns very slowly and with an odour of resin. The

percentage of cellulose in this enamel must be very small. Its rapidity of drying is no quicker than that of a cellulose acetate solution in tetrachlorethane, and it is highly inflammable.

Solvent mixtures of tetrachlorethane with various percentages of amyl phthalate, benzyl alcohol, tricresyl phosphate, etc., as above detailed, may be used for cellulose acetate with, in addition, small percentages of resin or canada balsam for application in the arts.

The fabric of the wings of aeroplanes is treated with solutions of cellulose acetate. It is water-resisting and renders the material taut. The acetate acts as a preservative. It is combustible but not explosive.—C. F. Cross, *Chem. & Drugg.*, /1917, 252.

DOPE. The name given to a solution of cellulose acetate or celluloid in tetrachlorethane with amyl alcohol and benzene. Poisoning from inhalation of fumes.—See W. H. Wilcox, *Lancet* i/1915, 544, also W. E. Lee, *Lancet*, /1916, 24.

VISCOSE. Its use for capping bottles, etc.—C. F. Cross., *Chem. & Drugg.*, /1917, 252.

Acetyl artificial silk is more transparent than protein products, such as silk or wool, to ultra-violet light.—L. Hill, *Brit. med. J.*, ii/1925, 473.

GRANATI RADICIS CORTEX

Granati Radicis Cortex (*B.P.C.* '34). Contains not more than 2% of wood or other foreign organic matter. The limit for Granatum, *U.S.P. X*, is the same. Cortex Granati, *P.G. VI*, should yield not less than 0.4% of alkaloid. Cortex Granati, *P. Helv. V*, is standardised to yield not less than 0.5% of alkaloid.

Pelletierinæ Tannas (*B.P.* '32). Residue on ignition, not more than 0.1%. An acidified solution yields no precipitate with platinic chloride solution. Pelletierinæ Tannas, *U.S.P. X*, should yield not less than 20% of residue by extraction with chloroform from alkaline solution, evaporation with 0.1 ml. of hydrochloric acid, and drying for one hour at 60°.

GUARANA

Guarana (*B.P.C.* '34). Contains not less than 3.5% of caffeine, calculated as anhydrous. Assayed by maceration with chloroform and ammonia, evaporation of an aliquot part of the filtered solution, solution of the residue in warm N/5 sulphuric acid and extraction of the filtered liquid, made alkaline with sodium hydroxide, with chloroform, finally evaporating and drying at 100°. Guarana, *N.F. V*, yields not less than 4% of caffeine dried at 80°, by a similar extraction.

HEXAMINA

Hexamina (*B.P.* '32). $C_6H_{12}N_4 = 140.1$. Contains not less than 99% of $C_6H_{12}N_4$. Ash, not more than 0.05%. Assayed by boiling with N/1 sulphuric acid until all the formaldehyde produced has been evolved, and back titrating the excess acid with N/1 sodium hydroxide to methyl orange. By the same method Methenamina, *U.S.P. X*, should contain 99% of the pure substance.

A tentative quantitative method for the determination of hexamine in tablets is described in Methods of Analysis (A.O.A.C., 1930, 456).

Experiments on the Use of Hexamine in Bacilluria. The following experiments were conducted by W. H. Martindale in order to determine which of the following—hexamine itself, formaldehyde set free therefrom in an acid urine, or even the acid sodium phosphate alone, used to increase the acidity of the urine, is the active agent in overcoming bacilluria.

The amount of formaldehyde passed in the urine by a patient taking a drug of the nature of hexamine, even if split up, would be small compared with the volume of the urine.—*cf. Analytical Memoranda chapter.*

Hexamine is in itself non-bactericidal. Martindale substantiated that even a 10% solution would not kill *B. coli in vitro* (*cf. Antiseptic Powers chapter*). In this connection it should be added that the salicylate (Vesalvine "S") is more potent on *B. Coli*. It kills in 2½% solution within 30 minutes. It should be noted that:—

(1) Hexamine is in reality a stable compound. It is only very slightly decomposed into formaldehyde at body temperature. It needs *boiling* with mineral acid to decompose it quickly—or prolonged warmth at 40° as mentioned in Vol. I, p. 450.

(2) The experiments showed that 2% formaldehyde (=5% of the solution) would have to be present in the bladder and other organs to sterilise the urine promptly. This quantity is never present on taking even a number of 10 grain doses of hexamine.

There were therefore grounds for the view that the useful effects of hexamine could not be due to the small amount of formaldehyde set free.

It is known that a patient with bacilluria and a relatively low acid index (e.g., 2° or less), taking hexamine alone, fails to improve, but if sodium acid phosphate be given simultaneously bacteria diminish as the degree of acidity rises. The high acidity, however, cannot be kept up for long, as it causes intense discomfort.

The following specimens of urine were, therefore, inoculated with *B. coli* and loopfuls transferred to MacConkey's broth after 2½ minutes, 30 minutes, and 3 hours contact; the urines themselves were then incubated and loopfuls transferred to MacConkey's culture medium after 18 hours incubation:—

(1) Urine alone with Acid Index = 0·7, as control

(2) Urine with sodium acid phosphate to make Acid Index = 6°

(2a) " " " " " " " " = 3°

(2b) " " " " " " " " = 1½°

(3) Urine Acid Index 6° (No. 2 urine) + "hexamine" 0·13%

(4) Urine Acid Index 0·7 (No. 1 urine) + "hexamine" 0·13%

(This amount of hexamine—0·13%—is such as would possibly be present in the bladder—1500 ml. content—after 2 doses of 1 gramme). *Not one inhibited the organisms after three hours' contact. After 18 hours' incubation* No. 3 urine was quite bright, but all the rest showed strong growth. Inoculation of MacConkey's broth showed that No. 3 was sterile, all the rest giving growth. No. 3 gave a distinct reaction for formaldehyde by Rimini's test, No. 4 gave none. This proves that although the proportion of formaldehyde is insufficient to kill *B. coli*, nevertheless, the small amount slowly generated from the hexamine is sufficient to inhibit growth of the organisms and thereby to have marked influence on bacilluria.

Sterilisation of Hexamine Solutions. 15% and 40% solutions containing respectively, prior to heating, 6 and 16 parts of formaldehyde per million, showed a content of 100 and 200 parts after 20 minutes at 100°. In the case of 15% solution the amount of formaldehyde is 1 in 10,000 or 1/60 grain in 10 ml.

HYDRARGYRUM

Hydrargyri Cyanidum (B.P.C. '34). $C_2N_2Hg = 252\cdot6$. Contains not less than 99% of $Hg(CN)_2$. Residue on ignition not more than 0·1%. Limit tests for mercuric chloride and mercuric oxycyanide are described. Assayed by addition of sodium chloride and potassium iodide, and titration with N/1 hydrochloric acid to methyl orange.

Carbasus Hydrargyri et Zinci Cyanidi (*B.P.C.* '34). Double Cyanide Gauze contains mercury equivalent to from 0.5% to 1.5% of $\text{Hg}(\text{CN})_2$, and zinc equivalent to from 1.5% to 3% of $\text{Zn}(\text{CN})_2$. A nitric acid extract of the gauze and washings is adjusted to volume; zinc is determined in one portion by the *B.P.* method for Zinci Sulphas, by precipitation with mercuric ammonium thiocyanate solution and subsequent titration with potassium iodate; mercury is precipitated as sulphide from the remaining portion after neutralisation and just acidifying with hydrochloric acid.

Hydrargyri Iodidum Flavum (*B.P.C.* '34). $\text{HgI} = 327.5$. Assayed by interaction with N/10 iodine and potassium iodide, followed by back titration with N/10 sodium thiosulphate; a purity of the dried substance of not less than 99% should be indicated. Loses not more than 0.5% on drying over sulphuric acid, and leaves not more than 0.2% of residue on volatilisation. The *U.S.P. X* specifies that the substance dried over sulphuric acid shall contain 99% of HgI ; residue on volatilisation at about 300° , not more than 0.2%.

Hydrargyri Iodidum Rubrum (*B.P.* '32). $\text{HgI}_2 = 454.5$. After standing for ten minutes with zinc powder and water and filtering off the amalgam formed, the filtrate and washings are treated with excess N/10 silver nitrate and nitric acid and titrated with N/10 ammonium thiocyanate; not less than 99% of the pure salt should be indicated. Leaves not more than 0.1% of residue on volatilisation. The *U.S.P. X* uses the electrolytic method of assay and requires the substance dried over sulphuric acid to contain not less than 99% of HgI_2 .

Solvellæ Hydrargyri Iodidi (*B.P.C.* '34). Contain 8.75 grains of HgI_2 , and one tablet in a pint of water gives a 1 in 1000 solution of HgI_2 . Some makers prepare them to contain $8\frac{3}{4}$ grains of anhydrous mercuric potassium iodide (HgI_2, KI) with a sufficiency of potassium iodide in excess to make the body $\text{HgI}_2, 2\text{KI}$. One dissolved in 1 pint of water makes a 1 in 1000 solution of mercuric potassium iodide and each contains 6.4 grains of HgI_2 . A trade custom has developed, however, of making them on various assumptions, e.g., to contain $8\frac{3}{4}$ grains of the soluble iodide, $\text{HgI}_2, 2\text{KI}$, which renders the content of mercuric iodide in the solution far less, namely, 5 grains.

To estimate the mercury in tablets of this kind, formalin reduction as recommended by E. Rupp is used. For the iodine, the iodate reaction in presence of strong hydrochloric acid is suitable. $2\text{HI} + \text{HIO}_3 + 3\text{HCl} = 3\text{ICl} + 3\text{H}_2\text{O}$. The whole matter is well dealt with in a paper by A. J. Jones, *Chem. & Drugg.*, i/1920, 523.

A tentative quantitative method for the determination of mercuric iodide in tablets is described in *Methods of Analysis (A.O.A.C., 1930, 461)*.

Hydrargyri Oxidum Flavum (*B.P.* '32). $\text{HgO} = 216.6$. Loses not more than 1% when heated at 150° for one hour, and then contains not less than 99.3% of the pure substance. Residue on ignition, not more than 0.5%. Assayed by titration in nitric acid solution with N/10 ammonium thiocyanate. The *U.S.P. X* requires the substance dried to constant weight at 150° to contain 99.5% of HgO .

The temperature of 150° , specified in the *B.P.* as that at which the substance is to be dried for calculating the percentage strength, is too high since marked amounts of mercurous oxide are produced at this temperature. This decomposition and that of the mercurous oxide occurring as an impurity can be minimised by drying at 70° , at which temperature no decomposition takes place.—G. J. W. Ferrey, *Quart. J. Pharm.*, 1933, 406.

Hydrargyri Oxidum Rubrum (*B.P.C.* '34). $\text{HgO} = 216.6$. Loses at 150° not more than 1%, and is then of 99.3% purity. Residue on volatilisation, not more than 0.3%. The *N.F. V* requires the similarly dried salt to contain not less than 99.5% of HgO .

Hydrargyri Oxycyanidum (*B.P.* '32). $\text{HgO}, 3\text{Hg}(\text{CN})_2 = 974.5$. Contains 20% to 22% of HgO and 77% to 79% of $\text{Hg}(\text{CN})_2$. Loss at 100° , not more than 1%. Residue on ignition, not more than 0.1%. Assayed for mercuric oxide by treatment with sodium chloride and titration with N/10 hydrochloric acid to methyl orange; and for mercuric cyanide by continuing the titration after adding potassium iodide.

Hydrargyrum oxycyanatum, *P.G. VI*, contains 33.3% to 35.2% of $\text{Hg}(\text{CN})_2, \text{HgO}$, corresponding to 15.37% to 16.25% of HgO and 84.6% to 83.8% of $\text{Hg}(\text{CN})_2$. Hydrargyrum oxycyanatum, *P. Helv. V*, contains from 15.37% to 16.25% of HgO and from 83.75% to 84.63% of total $\text{Hg}(\text{CN})_2$.

Since the official statement of solubility may be taken as evidence of conformity or otherwise with the requirements of the *B.P.*, it seems desirable to modify the official test as follows:—One part should readily dissolve in eighteen parts of boiling water with only a trace of residue, and the liquid should remain clear when cooled to 15.5° .—F. C. J. Bird, *Quart. J. Pharm.* 1934, 581.

The pure substance $\text{HgO}, \text{Hg}(\text{CN})_2$ is dangerous. It may explode at 180° or during drying or grinding.

Hydrargyri Perchloridum (*B.P.* '32). $\text{HgCl}_2 = 271.5$. Contains not less than 99.5% of the pure salt. Residue on volatilisation, not more than 0.1%. Assayed by reduction in presence of potassium iodide with formaldehyde and sodium hydroxide solutions, acidifying with acetic acid and adding excess N/10 iodine and, when the precipitate is completely dissolved, back titrating with N/10 sodium thiosulphate. Hydrargyri Chloridum Corrosivum, *U.S.P. X*, after drying to constant weight over sulphuric acid should contain not less than 99.5% of HgCl_2 . Assayed by precipitation as sulphide, washing and drying at 110° .

In the *B.P.* assay process the addition of 5 ml. of a mixture of 2 vols. of ether and 1 vol. of chloroform enables rapid solution of the precipitated mercury to be effected.—H. Brindle, *Quart. J. Pharm.*, 1932, 432.

Mayer's Reagent. (*Tanret's Reagent* is identical in composition. mercuric chloride 13.546 g., potassium iodide 49.8 g., distilled water to 1 litre. This reagent gives a precipitate with alkaloids.

Formerly, methods of volumetric estimation of alkaloids by means of the above were in vogue, but the composition of the precipitates is variable.

Liquor Hydrargyri Perchloridi (*B.P.* '32). Contains 0.095% to 0.105% *w/v* of mercuric chloride.

Hydrargyri Salicylas (*B.P.C.* '34). Contains from 54% to 59.6% of Hg . Residue on gentle ignition at about 300° , not more than 0.2%. Assayed by acidifying with acetic acid a solution of the substance in N/1 sodium hydroxide and standing with N/10 iodine for three hours, then titrating the excess iodine with N/10 sodium thiosulphate. The *U.S.P. X* substance should contain from 54% to 59.5% of Hg ; determined by heating with sulphuric and nitric acids on a sand-bath until a colourless mixture results, diluting, and titrating with N/10 potassium thiocyanate. Hydrargyrum salicylicum, *P.G. VI*, contains not less than 92% of $\text{C}_6\text{H}_3(\text{OH})\text{COOHg}$.

Hydrargyri Subchloridum (*B.P.* '32). $\text{HgCl} = 236.1$. Should contain not less than 99.6% of the pure substance. Residue on volatilisation, not more than 0.1%. Assayed by dissolving in water with potassium iodide and titrating with N/10 hydrochloric acid to methyl orange. Hydrargyri Chloridum Mite *U.S.P. X*, after drying to constant weight over sulphuric acid, contains not less than 99.6% of HgCl . Determined by interaction with iodine and potassium iodide and titration of the excess iodine with sodium thiosulphate.

Finely Divided Calomel (*Duret*). Dissolve sodium bicarbonate 6 g. and glucose 10 g. in distilled water 80 ml. Then dissolve separately magnesium chloride cryst. 7.5 g. in water 20 ml. Mix the above and add to a third solution consisting of mercuric chloride 11.5 g., hydrochloric acid 10 drops and water 100 ml. Shake well and allow to stand. Carbon dioxide is evolved. When this slackens, warm on a water-bath until no more gas comes off; wash and dry the precipitate. Yield, 10 g. of a light form of calomel, which may be more active for local use.

Calomel made by this formula is similar to the scaly calomel recommended by Burdon Cooper some years ago for ophthalmic use.

An official quantitative method for the determination of mercurous chloride in tablets is described in *Methods of Analysis* (*A.O.A.C.*, 1930, 481). A tentative quantitative method for the determination of mercurous chloride in calomel ointment is also described.

Hydrargyrum (*B.P.* '32). $\text{Hg} = 200.6$. Assayed by titration of the solution in nitric acid with ammonium thiocyanate; should contain not less than 99.5% of Hg . Residue on volatilisation at about 300° , not more than 0.02%. The *U.S.P. X* standard is the same.

Mercury, Detection of in Human Hair. An amount corresponding to 1 in 90,000,000 can be found, using 2 to 10 g. of the hair, in those who have undergone mercurial treatment.

Free the specimen from grease by washing with ether, alcohol, and water and digest in hydrochloric acid containing potassium permanganate. O

Complete solution treat with H_2S . Collect the precipitate and treat with potassium chlorate and hydrochloric acid. Filter, evaporate to small bulk and boil gently a strip of copper foil in the liquid. Dry the foil and place in a tube one end of which ends in a capillary. Exhaust and seal, then heat in a flame so as to sublime the mercury in the capillary. Globules may then be seen under the microscope.

Hydrargyrum cum Creta (B.P. '32). Contains from 31% to 35% of mercury. Hydrargyrum cum Creta, U.S.P. X, contains from 37% to 39% of Hg.

The B.P. assay process gives low and erratic results. The amount of nitric acid should be doubled, and after boiling for five minutes the liquid should be treated with potassium permanganate solution until pink, then decolorised with ferrous sulphate and titrated with thiocyanate.—W. J. Beardsley and J. J. Styles, *Quart. J. Pharm.*, 1934, 541.

If potassium permanganate is added no increase in the nitric acid is necessary. Hydrogen peroxide may be used instead of ferrous sulphate.

Mercury in a finely divided state is rapidly oxidised and a limit for mercuric mercury should have been included.—*Pharm. J.*, ii/1932, 106.

Unguentum Hydrargyri (B.P. '32). Assayed by boiling with nitric acid and water, filtering, adding potassium permanganate to a faint pink coloration, followed by decolorisation with ferrous sulphate and titration with N/10 ammonium thiocyanate; it should contain from 29% to 31% of mercury. Unguentum Hydrargyri Fortius, U.S.P. X, contains 49% to 51% of Hg, and Unguentum Hydrargyri Mite, U.S.P. X, contains 29% to 31% of Hg.

Assay of Mercurial Ointments. The method recommended for the assay of mercury or one of its compounds in ointments, when it is distributed through, but not chemically combined with, the basis, consists of dissolving the basis in xylol in a centrifuge tube, and centrifugally separating out the suspended solid. Most of the liquid is now syphoned off, and the process repeated twice with fresh portions of solvent, replacing the xylol after the first time with light petroleum. A layer of alcohol is now interposed between the deposited solid and the petroleum layer. The mixture is centrifuged again, and the petroleum layer, along with some of the alcohol, drawn off. Either the residual alcohol is now evaporated off, the solid dissolved in nitric acid, transferred to a flask and titrated with ammonium thiocyanate, or the mixture is shaken, the alcoholic suspension rinsed into a flask, and the assay of the salt completed by the official or other suitable process.—W. R. Heading, *Quart. J. Pharm.*, 1934, 406.

Method for Strong Ointment of Mercuric Nitrate. Heat the ointment with 50% aqueous potassium hydroxide for about 35 minutes in the presence of zinc dust. The mercury is set free first as mercuric oxide, which is then reduced to metal by the hydrogen generated from the action of the alkali on the zinc. An amalgam is formed with the excess of zinc, and the mercury is thus obtained quantitatively in a granular form, which may easily be freed from soap by decantation, filtration and washing. The amalgam is next dissolved in nitric acid, and the mercury determined by means of ammonium thiocyanate, the presence of zinc as nitrate being quite without effect.—W. R. Heading, *Quart. J. Pharm.*, 1934, 413.

The official method may be modified with advantage by substituting titration with standard thiocyanate solution for gravimetric determination of the mercury as sulphide.

To about 5 g. in a long-necked flask of about 250 ml. capacity add 35 ml. of sulphuric acid, and heat cautiously until the mixture darkens. Add gradually 5 ml. of fuming nitric acid, rotating the flask to assist the escape of evolved gases. Heat, and maintain just below the boiling point. Repeat several times the addition of fuming nitric acid and the heating, until an almost colourless solution remains. Cool, add a slight excess of solution of potassium permanganate and heat to boiling. Add sufficient solution of hydrogen peroxide to make the solution colourless, cool and dilute to 250 ml. Titrate 100 ml. with N/10 ammonium thiocyanate, using solution of ferric ammonium sulphate as indicator.—C. H. Hampshire and G. R. Page, *Quart. J. Pharm.*, 1935, 75.

Unguentum Mercuriale (B.P.C. '34). Contains 33.3% of Unguentum Hydrargyri with lard.

Hydrargyrum Ammoniatum (B.P. '32). $\text{NH}_2\text{HgCl} = 252.1$. Contains not less than 97% and not more than the equivalent of 100.5% of NH_2HgCl . Residue on ignition at a low red heat, not more than 0.2%. Assayed by treatment

with potassium iodide and titration to methyl orange with N/10 hydrochloric acid. The *U.S.P. X* substance is assayed for Hg content by precipitation as sulphide, and should contain HgNH_2Cl equivalent to from 78% to 80% of Hg.

Hydrargyrum præcipitatum album, *P.G. VI*, contains the equivalent of not less than 98.3% of NH_2HgCl . **Hydrargyrum præcipitatum album**, *P. Helv.*, is assayed by the following process:—Mix 0.2 g. with about 50 ml. of water and 2 g. of sodium thiosulphate and shake frequently during 10 minutes until dissolved; add 2 or 3 drops of methyl orange and titrate with N/10 hydrochloric acid. 1 ml. of N/10 HCl is equivalent to 0.012604 g. of HgClNH_2 .

Hydrargyrum Oleatum (*B.P. '32*). Should contain the equivalent of from 19% to 21% of yellow mercuric oxide. Assayed gravimetrically by precipitation as sulphide from a solution in benzene, glacial acetic acid and alcohol. **Oleatum Hydrargyri**, *U.S.P. X*, is prepared with 25% of yellow mercuric oxide.

Mercurochromum (*B.P.C. '34*). Loses on drying *in vacuo* at 50° over sulphuric acid, not more than 10% and then contains from 25% to 28% of Hg and from 21% to 23% of Br. Limit tests for free mercury, soluble mercury salts and sodium are described. Hg is estimated by separation as the zinc amalgam which is then dissolved in nitric acid and treated with urea, the oxidised solution being titrated with N/10 ammonium thiocyanate; assayed for Br content by titration of the product of the fusion with potassium nitrate and potassium and sodium carbonates, with silver nitrate and ammonium thiocyanate. The *B.P.C. '34* has introduced a standard consisting of a quantity of mercurochrome kept by the Pharmaceutical Society and supplied on request. It is required that mercurochrome for intravenous injection shall not be more toxic than the standard sample. Manufacturers preparing mercurochrome are expected to determine the average lethal dose of the standard mercurochrome for mice under the conditions of their own laboratory. This dose, which kills 50% of mice, must be determined with care. Mice are then injected with the unknown sample, using the above determined dose. Ten mice are first injected; and if not more than two die, the sample passes the test. If more than two die, ten more are injected. If out of the twenty injected not more than eight die, the sample passes the test. If more than eight but less than fifteen die, ten more mice are injected, and the sample passes the test if the number of deaths is not greater than fifteen out of the thirty mice injected.

Alkaline-Permanganate Oxidation Assay. The results obtained by the *B.P.C.* method for the assay of mercury show an appreciable experimental variation. The following alkaline-permanganate oxidation method appears to give more reliable and consistent results:—

Dissolve 0.5 g. of mercurochrome in 50 ml. of water in a 600 ml. beaker, add 10 ml. of 40% caustic soda solution and 2 to 3 g. of potassium permanganate and boil gently over a micro-burner for 15 minutes. Cool slightly and add gradually a cooled mixture of 10 ml. of concentrated sulphuric acid and 200 ml. of water, avoiding loss by spurting by covering the beaker with a clock glass. Allow to cool, and add in small portions, with rapid stirring, a slight excess of 10 vols. hydrogen peroxide. Replace over the micro-burner, add excess of 5% potassium permanganate solution and ensure an excess after boiling gently for 10 minutes. Add dilute oxalic acid solution, drop by drop, until a water-white solution is obtained. Precipitation of the mercury as sulphide with subsequent filtration and weighing is carried out by the usual routine. R. F. Corran and F. E. Rymill, *Quart. J. Pharm.*, 1935, No. 3.

The various specimens on the market differ markedly in chemical composition. Toxicity appears to bear a direct relationship to purity, and the nearer the composition approximates to theoretical requirements the better the therapeutic efficiency and the lower the toxicity. A 1% solution frequently gives rise to mercurial poisoning, but a 0.4% solution is relatively free from this objection. John Eyre and Sir W. J. Pope, *Brit. med. J.*, ii/1928, 239.

Antiseptic Efficiency. Mercurochrome cannot be relied upon to destroy bacteria that have penetrated into the living tissue of a wound or of the skin; it could do no more than disinfect the surface and the necrotic tissue—a limitation shared by all antiseptics. The antiseptic efficiency of mercurochrome is not outstanding, and for skin disinfection the aqueous solution is distinctly inferior, though the absence of irritation may be an advantage.—W. F. von Oettinger and co-workers (for the Council on Pharmacy and Chemistry, Amer. Medical Ass.), *J. Amer. med. Ass.*, ii/1932, 134.

HYDRASTIS

Hydrastis (*B.P.C.* '34). Foreign organic matter, not more than 2%. Acid-insoluble ash, not more than 3%. Hydrastis, *U.S.P. X*, should contain not more than 2% of its stems and leaves, and not more than 2% of other foreign organic matter; and should yield not less than 2.5% of ether-soluble alkaloids of hydrastis and not more than 3% of acid-insoluble ash. It is assayed gravimetrically by maceration with ether, shaking an aliquot part with acid and transferring the alkaloids to ether. Rhizoma Hydrastis, *P.G. VI*, yields not less than 2.5% of hydrastine.

Hydrastinæ Hydrochloridum (*B.P.C.* '34). $C_{21}H_{21}O_6N, HCl = 419.6$. Loss at 100°, not more than 6%. Ash, not more than 0.1%. Limit tests for hydrastinine and berberine are included. The *N.F.V* also includes these tests.

Hydrastininæ Hydrochloridum (*B.P.C.* '34). $C_{11}H_{12}O_2NCl = 223.5$. Ash, not more than 0.1%. Tests for limit of foreign alkaloids and hydrastine are described.

Hydrastine (Alkaloid). To distinguish from hydrastinine:—A solution of about 0.1 g. in 10 ml. of dilute sulphuric acid shows no blue fluorescence, but on gradually adding potassium permanganate solution, 1 in 10, avoiding excess, the fluorescence develops.

HYOSCYAMUS

Hyoscyamus (*B.P.* '32). Contains not less than 0.05% of the alkaloids of hyoscyamus, calculated as hyoscyamine, not more than 1% of foreign organic matter and not more than 1% of stems more than 5 mm. in diameter. Ash limit, 20%. Acid-insoluble ash limit, 12%. Assayed by maceration and percolation with ether-alcohol (4 : 1) mixture with the addition of ammonia; the percolate is extracted first with hydrochloric acid and then with portions of 1/10 hydrochloric acid and alcohol mixture (3 : 1); the neutralised acid liquids are evaporated *in vacuo*, not above 40°, to small bulk, and subsequently made ammoniacal and extracted with chloroform; the alkaloid is finally dried at 80° for 2 hours to remove volatile bases, and titrated to methyl red or cochineal. Hyoscyamus, *U.S.P. X*, should yield by the ether-chloroform (3 : 1) percolation process, with final extraction with chloroform and titration without previous heating, not less than 0.065% of alkaloids of hyoscyamus; it contains not more than 25% of its stems, none being more than 5 mm. in diameter; acid-insoluble ash, not more than 12%.

Folia Hyoscyami, *P.G. VI*, yields not less than 0.07% of hyoscyamine. Folium Hyoscyami, *P. Helv. V*, consists of the leaves of the flowering plant of *Hyoscyamus niger* Linn., without stem, fruits or flowers, and contains not less than 0.05% of alkaloid. It may yield up to 20% of total ash and up to 6% of acid-insoluble ash. Herba Hyoscyami mutici, *P. Helv. V*, from *Hyoscyamus muticus* Linn., contains not less than 0.8% of alkaloids and is used for making extract and tincture of hyoscyamus.

Cultivation. Hyoscyamus seed from wild plants germinated well and gave a biennial crop, while commercial seed was not good.—T. W. Hazelby, *Pharm. J.*, 1921, 227.

If the whole of the seeds of a biennial plant are saved and sown, the seed will consist of a mixture of different sizes, some being small and brown in colour. The latter are usually immature and will, when dried, float on water. These may be thrown away. If the seeds are sifted, there will be a considerable proportion of smaller grey seeds. These produce the annual plants and the larger seeds produce the biennial plants. Note chemical analysis of the plant solids—phosphoric acid 44, magnesium 21, potassium 18, lime 6, sodium 1. The excess of magnesium over calcium is rather unusual and explains the liking for the sea shore and for magnesian soils (öolite, etc.) inland. Directions for culture.—E. M. Holmes, *Pharm. J.*, i/1921, 249.

The root is richest in total alkaloids and the annual plant is, if anything, a trifle richer than the biennial leaves either of the first or second year: thus biennial root, 0.16%; leaves, biennial first year, 0.059% to 0.069%; leaves and tops, second year, 0.065% to 0.068%; leaves and tops, annual, 0.064% to 0.07%.—S. Jensen, *Pharm. J.*, i/1915, 98.

Hyoscinae Hydrobromidum (*B.P.* '32). $C_{17}H_{21}O_4N, HBr, 3H_2O = 438.1$. M.p., after drying at 100° , 194° to 196° . Specific rotation determined in 5% w/v aqueous solution of the anhydrous salt, -24° to -26° . Loss at 100° , 12% to 13%. Ash, not more than 0.1%.

Hyoscyaminae Hydrobromidum (*B.P.C.* '34). $C_{17}H_{23}O_3N, HBr = 370.1$. Loss at 100° , not more than 1%. Ash, not more than 0.1%.

Hyoscyaminae Sulphas (*B.P.C.* '34). $(C_{17}H_{23}O_3N)_2, H_2SO_4 = 676.5$. M.p. not below 203° . Loss at 100° , not more than 1%. Ash, not more than 0.1%.

ICHTHAMMOL

Ichthammol (*B.P.* '32). The dried substance contains not less than 10.5% w/w of organically combined sulphur, and not more than 12.5% of sulphur in the form of sulphates than one-fourth of the total sulphur. Loss at 100° , not more than 50% by weight. Residue on ignition and re-ignition with sulphuric acid, not more than 0.3%. Assayed for total sulphur by gentle ignition with sodium carbonate and copper nitrate, dispersion of the ichthammol in the sodium carbonate having been effected by evaporation with chloroform, followed by precipitation as barium compound and ignition: assayed for sulphates by precipitation of a solution with cupric chloride solution, filtration and precipitation with barium chloride; organically combined sulphur is obtained by the difference between these two percentages.

Ammonium sulfobituminosum, *P. Helv. V*, contains 1.2% to 4.2% of total ammonia, not more than 1.7% of sulphur as sulphate and not less than 7.25% of total sulphur. The difference between the percentage of total sulphur and the sum of the sulphur as sulphate and the sulphur as sulphonic sulphur, gives the percentage of organically combined sulphur, which should not be less than 4%.

INSULINUM

Insulinum (*B.P.* '32). Complies with tests for sterility, and the solution contains 20 units per millilitre. Controlled by regulations of the Therapeutic Substances Act, 1925. The standard preparation for Great Britain and Northern Ireland is a quantity of dry soluble insulin hydrochloride prepared and kept

the National Institute for Medical Research, London. The unit is the specific activity contained in such an amount of the standard preparation as the Medical Research Council may indicate as the quantity exactly equivalent to the unit accepted for international use. Crystalline insulin contains approximately 4,000 units per gramme.

BIOLOGICAL METHODS OF ASSAY

Rabbit Method. The rabbit method described in the *B.P.*'32 depends on the observation that a dose of about 1 unit of insulin injected under the skin of a fasting rabbit causes a fall in the blood sugar which is greatest after 2 to 3 hours, the concentration returning to the normal value after 5 hours. If the initial percentage of blood sugar is observed, and also the percentage at the end of each hour for 5 hours after injection, a figure for the hypoglycæmic effect can be calculated. This is done by taking the average figure for the 5 hours after injection, and subtracting it from the initial figure. The result is then expressed as a percentage of the initial figure and is called the percentage blood sugar reduction.

In performing the test, twelve rabbits of about 2 kg. weight, which have been without food for 24 hours, are used. Six are injected with 1 unit of the standard preparation, and six with a quantity of the unknown sample expected to contain 1 unit. The percentage blood sugar reduction is then determined for each rabbit. Two days later, the experiment is repeated on the same animals; the rabbits which before received the standard now receive the unknown, and those which received the unknown now receive the standard. There are now two figures available for each rabbit, namely the percentage blood sugar reductions when injected with the standard and those when injected with the unknown. The average figure given by all the rabbits for the percentage blood sugar reduction after injection with the standard is then compared with that after injection with the unknown preparation. If the dose of the unknown preparation was correctly chosen the two figures should be equal. If they differ appreciably the experiment must be repeated, using a different dose of the unknown.

Mouse Method. The mouse method depends on the appearance of convulsions in mice after they are injected with insulin. A large group of mice is taken, of which one half receives a dose of the unknown preparation, the other half receiving the standard. The percentage of mice in each group in which convulsions occur is then determined, and, from the result, the potency of the unknown can be stated in terms of that of the standard.

The mice are prepared by being kept without food overnight. They are injected and placed immediately in a thermostat kept at a temperature which is usually 29° or 34°. Symptoms, which may be those of collapse or of convulsions, occur within 2 hours, and the proportion of mice showing symptoms is determined. In deciding the potency of the unknown preparation in relation to that of the standard, two doses of the standard are used, one of which causes a higher percentage of convulsions than that caused by the unknown, while the other causes a lower percentage. The dose of the unknown can then be equated to the mean of the two doses of the standard. Alternatively, the relative potency of unknown and standard can be determined from the percentages of convulsions by using a previously determined curve relating dose to percentage convulsions.

INSULIN NOT A "FINE CHEMICAL" within the meaning of the Safeguarding of Industries Act. By the word "chemical" the Act intended bodies made by ordinary chemical methods, and in order to be "fine chemicals" the methods by which they were produced must be methods of accuracy and the substances must be either one body, or, if more than one, a perfectly ascertained combination, not an indefinite group. The argument of the defending counsel, reinforced by the Board of Trade, was that it was not intended to include any article in the definition "fine chemicals" unless it was something the identity of which was as certain as could be reasonably expected, and that it was not yet generally accepted that insulin came within that category. (Board of Trade enquiry arising from a complaint by the Association of British Chemical Manufacturers and four drug houses that insulin and its salts had been improperly excluded from the list of articles chargeable with duty under the Act, the opposing party being the agent for a Danish firm of exporters).—*British med. J.*, ii/1933, 989.

A majority of members of the Tribunal decided that "Insulin and its salts should be added to the list H iii under Sect. 1 (5) of the Safeguarding of Industries Act as amended by the Finance Act, 1926, and the list was amended accordingly from December 14th, 1933.—*Brit. med. J.*, ii/1933, 1133.

The Customs duty on imported insulin was subsequently removed owing to representations that its imposition had resulted in the price being higher than it otherwise would have been, although less than that ruling when the duty was first imposed.—*Brit. med. J.*, i/1934, 1059.

IODUM

Iodum (*B.P.* '32). $I = 126.9$. By titration with $N/10$ sodium thiosulphate, it contains not less than 99.5% of I . Residue on volatilisation on a water-bath, not more than 0.05%. The same standard is required for Iodum, *U.S.P. X*.

Manufacture. The sea-weeds vary enormously in iodine content, and only *L. digitata* ("Tangle Stem") and *L. stenophylla* are worth burning for kelp. The varieties known collectively as *drift kelp* are richer than cut kelp. If properly burnt, the drift weed ought to yield 25 to 30 lbs. of iodine per ton. 12 lb. per ton is, however, above the average for ordinary drift kelp. Very good Scotch kelp yields potassium sulphate 14%, potassium chloride 18%, sodium chloride 14%, sodium carbonate 4%, and iodine $14\frac{1}{2}$ lb. per ton. When burnt into "loose ash" these figures are respectively 13%, 18%, 6.8%, 3.4% and 28 lbs.

The mineral known as **caliche**, the crude sodium nitrate of Peru and Chili, forms now by far the most important source of iodine. It is present in the form of iodate. Sodium bisulphite is used to precipitate the iodine from the mother liquors from which the sodium nitrate has been crystallised. As the power of production of the factories on the spot is in excess of the world's power of consumption the makers have combined to restrict the output, iodine only being made for a few months during the year. The cost of recovering iodine as a by-product in this way is not more than $1\frac{1}{2}$ d. or 2d. per ounce.—Thorpe.

Laminaria extraction for iodine is still practised to some extent in Scotland. The dried weed contains about 0.55%. Kelp-burning is also practised in France, Japan and Ireland. It is not possible to extract more than 20% of the iodine contained in caliche. The International Combine, composed of the Chilean Association and the Scotch and French producers, *arranges* sales. World's output: long tons in 1925, Chili 983, U.K. 25, France 53, Japan 16.—*Imp. Inst. Brochure on Iodine*, 1928.

In the Black Sea, about the middle of the triangle formed by Sebastopol, Odessa and the mouth of the Danube, 30 to 50 metres below the surface, a spacious field of a red alga exists in which may be important quantities of iodine; likewise in the Sea of Azof.—*Pharm. J.*, i/1915, 41.

Red and chinook salmon contain four times as much iodine as butter, and undergo no apparent loss on canning. Canned salmon should be included in the diet of goitrous patients.—*J. Amer. med. Ass.*, i/1926, 1339.

Iodine in Natural Waters, see p. 475.

ESTIMATION OF ORGANIC IODINE COMPOUNDS. It is a good plan to saponify with KOH 2 g., water 12 ml. and alcohol 30 ml. After cooling, place in a separator and make acid with sulphuric acid; add chloroform and then a few drops of sodium nitrite solution. Shake and withdraw the chloroform, and then add a little more sodium nitrite and more chloroform, and so on until all iodine is removed. Wash with water, add sodium bicarbonate and titrate with $N/10$ sodium thiosulphate.—*Pharm. J.*, ii/1911, 711, *cf.*, Thyroid.

DETERMINATION OF IODINE VALUES OF OILS AND FATS

In the following methods, chlor-iodine addition products are formed of the glycerides of the unsaturated fatty acids and of the acids themselves that are contained in the oils so treated.

The iodine value indicates the percentage of iodine capable of absorption, and can be determined by the original method of Von Hübl, or by the more reliable and convenient modification proposed by Wijs.

Hübl's Method. The iodine solution is prepared by dissolving iodine 25 g. in 500 ml. of absolute alcohol, and also mercuric chloride 30 g. in a further 500 ml. of absolute alcohol, filtering and then mixing. After standing 12 hours or so, the strength is ascertained by standard sodium thiosulphate solution in the customary manner.

0.8 g. of the fat, or 0.4 g. of a non-drying oil, or 0.2 g. of a drying oil, is accurately weighed out by means of a weighing bottle or Sprengel tube, and dissolved in 10 ml. of chloroform or carbon tetrachloride in a 600 ml. stoppered bottle. The iodine solution, 25 ml., is run in from a pipette, and if the mixture becomes decolorised on standing a short time a further 25 ml. is added. After about 4 to 6 hours standing in the dark, 15 to 20 ml. of 10% potassium iodide solution is added and the liquid diluted with about 400 ml. of water. If there is any precipitate of mercuric iodide, more potassium iodide must be added. The free iodine is determined with N/10 thiosulphate and starch, shaking thoroughly. A blank experiment, without the oil, is conducted, and, from the difference in the two volumes of thiosulphate required, the amount of iodine absorbed can be calculated, and is expressed as units per cent. of the oil.

Example.—0.8 g. of a fat required 48—19 ml. of thiosulphate solution =
 29 ml. = 0.3651 g. iodine, therefore 100 of the fat combines
 with $\frac{0.3651 \times 100}{0.8}$ iodine = 45.6, which is therefore the iodine
 value of the fat.

B.P. '32 Method (Wijs' Method.) The iodine monochloride solution is prepared by,

(a) dissolving 13 g. of iodine in about 800 ml. of pure glacial acetic acid, and then passing in chlorine until the titre against thiosulphate is doubled. When this point is reached, there is a sharp change in colour from the brown to a brownish-yellow, and the solution is then made up to 1 litre with glacial acetic acid.

(b) Iodine trichloride 8 g.; iodine 9 g.; glacial acetic acid, sufficient to produce 1000 ml. Dissolve the iodine trichloride in about 200 ml. of glacial acetic acid; dissolve the iodine in about 500 ml. of glacial acetic acid; mix the two solutions, and add sufficient glacial acetic acid to produce the required volume.

Place the oil, or fat, accurately weighed, in a dry stoppered vessel, add 10 ml. of carbon tetrachloride, and dissolve. Add 20 ml. of solution of iodine monochloride, insert the stopper, previously moistened with solution of potassium iodide, and keep in a dark place at a temperature of about 17° for half an hour. Add 15 ml. of solution of potassium iodide and 100 ml. of water; shake, and titrate with N/10 sodium thiosulphate, using mucilage of starch as indicator. Note the number of millilitres required (a). At the same time carry out the operation in exactly the same manner, but without the substance being tested, and note the number of millilitres of N/10 sodium thiosulphate required (b).

Calculate the iodine value from the following formula:—

$$\text{Iodine value} = \frac{(b - a) \times 0.01269 \times 100}{\text{Weight (in grammes) of substance}}$$

The approximate weight, in grammes, of substance to be taken may be calculated by dividing 20 by the highest expected iodine value. If more than half the available halogen is absorbed, the test must be repeated on a smaller quantity of the substance being tested.

Pyridine-Sulphate-Bromide Method. Dissolve 8 g. of pyridine and 10 g. of sulphuric acid in 20 ml. of glacial acetic acid, keeping the mixture cool; add a solution of 8 g. of bromine in 20 ml. of glacial acetic and dilute to 1000 ml. with glacial acetic acid.

The oil or fat is dissolved in 10 ml. of chloroform, a small excess of the reagent is added and the mixture allowed to stand for 3 to 5 minutes. The excess of Br is determined either by adding potassium iodide solution and titrating with sodium thiosulphate or by direct titration with standard arsenite solution.—K. W. Rosenmund and W. Kuhnenn, per *Analyst*, 1924, 105.

This method is stated to give more consistent results than Wijs' method when the oil contains a high proportion of cholesterol.

Dichloramine has been used for the determination of iodine values and the results, within the limits of experimental error, agree with those obtained with Wijs' solution. The reagent is prepared as follows:—To a solution of 0.05 mol. of dichloramine in about 700 ml. of halogen stable acetic acid add 0.1 mol. of

dry powdered potassium iodide in small quantities at a time with continuous shaking. When all the iodide is dissolved, dilute to 1000 ml. with acetic acid.

The reagent may be stored in a bottle with a dark felt cover to minimise decomposition by light and to deter freezing. The iodine equivalent is determined in the usual way by determining the iodine liberated from a known volume of excess of aqueous potassium iodide.

HYDROGENATED FATS.—Determination of iso-oleic acid content permits recognition. This has iodine value of 90, and produces a lead salt insoluble in organic solvents.—*Pharm. J.*, i/1924, 537.

THIOCYANOGEN VALUE—a new constant of oils and fats—is of special use in determining the amount of linolic acid in an oil. Thiocyanogen, like iodine, is quantitatively absorbed by substances containing a double bond, but with fatty acids containing a triple bond (stearolic, behenolic) there is no absorption; and with linolic acid there is only absorption of half the thiocyanogen corresponding to its iodine value.—*Analyst*, 1926, 157, 264.

Iodised Oils. Iodinol, Lipiodol, etc., containing 40% of iodine, are employed to render the bronchi and their ramifications opaque to X-rays, their chief value lying in their ability to show the presence or absence of non-obstructive bronchiectasis, and when present, even in the early stages, its locality, extent, and type. They are non-irritant to the mucous membrane, etc. After injection in the bronchi, they are absorbed in the lung and iodine can be detected in the urine for many days after; hence they are antiseptic agents rational in the treatment of chronic affections of the lower respiratory tract.

Contraindications. High fever, marked intolerance to iodine, grave septic conditions of the lung, and active tuberculosis.

Method. Test first for iodine intolerance with potassium iodide, 10 grains, three times in the course of a day.

The amount used varies from 5 ml. to 40 ml., the average being 20 ml. For outlining the bronchial tree, 6 ml to 10 ml. is sufficient. (To lessen the viscosity the oil is first warmed in water at 100° F.)

Oral Use. Given the confidence and co-operation of the patient, this is best, but it is unsuitable in children and nervous patients. The patient should be seated with his head on his hand and his elbow on a rest, the operator in front. The tongue is protruded and a blunt-ended cannula placed over its base, between the pillar of the fauces and the uvula. The warm oil (100° F.) is given with a 20 ml. syringe, while the patient breathes slowly and regularly. If the patient heaves, it is useless to continue. He should lean to the side injected, and then be semi-recumbent with head lowered.

The Crico-thyroid Membrane Route. The patient reclines on a couch with head projecting over the end, to keep the membrane stretched. To inject the bases of the lungs, the shoulders must be kept raised, and for the apices the patient lies flat during the injection, the head and shoulders being lowered after. A drop of procaine solution to produce a small bleb is injected over the mid-point of the membrane exactly in mid-line. With a strong needle, 0.5 ml. of 5% solution of cocaine hydrochloride (warmed to 100° F.) is slowly injected through the spot into the trachea, and the patient can then sit up for 2 minutes and is allowed to cough. A 20 ml. syringe filled with the iodised oil is attached to a trochar and cannula which has been inserted into the trachea. To make sure the needle is in correct position, withdraw the piston; bubbles of air should freely enter the syringe. With the patient in the right position he should breathe deeply through the mouth, avoiding swallowing and coughing, the injection being given slowly. Radiograph quickly, vertically and horizontally, afterwards placing a collodion dressing on the spot. For the young or extremely nervous, a general anæsthetic (ethyl chloride, open method) is given. After every injection screen the stomach to ascertain whether much of the oil has been swallowed.

Other methods are direct injection into the lung, the Bronchoscopic, the Transglottic, the Intubation, the Catheter, and the "Swallowing" method.

Caution. There is an element of danger in the above technique, though with the oral method it is almost negligible. The procedure is a serious one and should not be employed indiscriminately. The possible dangers are symptoms of iodine poisoning (this only applies with the crico-thyroid route), injury to local tissues in the neck, and broncho-pneumonia resulting from dissemination of infection throughout the lung. Minor symptoms, which normally disappear in 24 hours, are injection malaise, anorexia, and headache. In pulmonary tuberculosis the injections are undesirable, and its use is dangerous in patients with advanced bronchiectasis with foul secretion.

The resulting pictures are excellent and there is no irritation of the mucous membrane.—F. G. Chandler, *Brit. med. J.*, ii/1928, 1157.

The injection of iodised oils is essentially a surgical procedure, introducing a foreign and possibly irritant body and involving more or less risk, which should be weighed against the presumptive advantages in comparison with the relative advantages and disadvantages of other measures. Cautions which should be specially borne in mind are (1) aged and darkened oils should never be used. (2) Subarachnoid injections should only be used when all other means of diagnosis have been exhausted. (3) Intratracheal and intrapleural injections should be avoided in tuberculosis of the respiratory organs. (4) Injection pressure should be carefully controlled so as not to lacerate tissues. (5) Intravaginal injections should only be made under fluoroscopic examination. (6) Iodised oil should not be used for renal pyelography except as an emulsion, and injections stopped if pain is felt. (7) Intravascular injections appear too dangerous.—Council on Pharmacy and Chemistry, A.M.A., *J. Amer. med. Ass.*, 1932, 1946.

X-RAY PICTURES OF THE MALE URETHRA.—Shadows obtained with Iodinol 0% very satisfactory. No irritation of the urethral mucous membrane. A urethral pouch demonstrated at the Midland Medical Society.—G. P. B. Luddy, June 6th, 1929.

For giving shadows of the uterus and fallopian tubes found satisfactory at Cardiff Royal Infirmary. No toxic symptoms.—W. Panes, June 20th, 1929.

For more recent references, see Vol. I, p. 515.

Liquor Iodi Aquosus (*B.P.C.* '34). Prepared to contain 5% *w/v* of iodine and 7.5% *w/v* of potassium iodide. *Liquor Iodi Compositus*, *U.S.P. X*, contains 4.8% to 5.2% *w/v* of I, and 9.8% to 10.2% *w/v* of KI. The potassium iodide is determined by the residue on evaporation and re-evaporation with water on a water-bath.

Liquor Iodi Fortis (*B.P.* '32). Contains from 9.8% to 10.2% *w/v* of iodine and 5.8% to 6.2% of potassium iodide. Iodine content estimated by titration with N/10 sodium thiosulphate and potassium iodate in presence of 40% of hydrochloric acid, and subtracting one half the thiosulphate titration. Alcohol content, 76% to 79% *v/v* of ethyl alcohol, decolorising with sodium thiosulphate and adding sodium hydroxide before distillation.

Liquor Iodi Mitis (*B.P.* '32). Iodine content, 2.45% to 2.55% *w/v*; potassium iodide content, 1.45% to 1.55% *w/v*. Alcohol content, 85% to 88% *v/v* of ethyl alcohol. *Tinctura Iodi*, *U.S.P. X*, contains 6.5% to 7.5% *w/v* of iodine and 4.5% to 5.5% *w/v* of KI; alcohol content, 82% to 84% *v/v*.

If the official solutions are deficient in potassium iodide, hydriodic acid is formed and would be calculated as potassium iodide in the *B.P.* assay process.—Magnus Herd, *Pharm. J.*, i/1934, 87.

Liquor Iodi Simplex (*B.P.* '32). Simple solution of iodine is prepared with 5% *w/v* of iodine in alcohol (95%). Owing to rapid reduction of the iodine it is standardised to contain from 8.8% to 9.2% *w/v* of *total* iodine.

When simple solution of iodine is stored the content of free iodine becomes constant in 8 months. The acidity of the solution still increases slightly after the free iodine content has become constant. A solution assaying 8.78% *w/v* of free iodine 7 days after preparation reached equilibrium at 7.17% of free iodine after storage for 8 months.—G. R. Page, *Quart. J. Pharm.*, 1935, 81.

Unguentum Iodi Denigrescens (*B.P.C.* '34). Prepared with arachis oil and yellow soft paraffin to contain 5% *w/w* of iodine. *Unguentum Iodi*, *B.P.C.* '34, contains 4% of iodine with potassium iodide and water in simple ointment.

Assay. The following method for the determination of iodine in iodised ointments may be used for the assay of iodine in non-staining iodine ointments:—About 1 g. of the sample, accurately weighed, is boiled for one hour under a reflux condenser with 10 ml. of glacial acetic acid and 1 g. of zinc filings. 30 ml. of hot water is added down the condenser tube, the liquid is filtered through a plug of wet cotton wool, and the flask and filter are washed with two portions of 10 ml. of water. The combined filtrate and washings (the filtrate need not be clear) are cooled, 100 ml. of hydrochloric acid is added, and the liquid is treated with M/20 potassium iodate, chloroform being added as indicator towards the end of titration, and titration being continued until, after vigorous shaking, the chloroform is colourless, the aqueous liquid being clear yellow. Each millilitre of M/20 potassium iodate is equivalent to 0.01269 g. of I.—J. T. Cocking and G. Middleton, *Quart. J. Pharm.*, 1931, 176.

IPECACUANHA

Ipecacuanha (*B.P.* '32). Contains not less than 2% of the total alkaloids of ipecacuanha, calculated as emetine, of which not less than two-thirds consists of non-phenolic alkaloids, calculated as emetine; and contains not more than 5% of stems, and not more than 1% of foreign organic matter. Ash, not more than 5.5%. Assayed for total alkaloids by maceration and percolation with ether-chloroform (3 : 1), transferring to acid solution, first with N/1 sulphuric acid and then with portions of N/10 acid and alcohol (3 : 1), finally extracting with chloroform from ammoniacal solution, determining the alkaloids by titration using methyl red or cochineal indicator; assayed for non-phenolic alkaloids by extraction of the titration liquid, made alkaline with sodium hydroxide, with ether and, after evaporation, titration of the alkaloids. *Ipecacuanha, U.S.P. X*, should contain not less than 1.75% of ether-soluble alkaloids of ipecacuanha, not more than 5% of its overground stems, or more than 2% of other foreign organic matter. Assayed by maceration with ether and extraction of an aliquot part, using ether for the final extraction of the alkaloids.

Radix Ipecacuanhæ, P.G. VI, yields not less than 1.99% of alkaloid, calculated as emetine. *Radix Ipecacuanhæ, P. Helv. V* contains not less than 2% of alkaloid soluble in ether. *Assay*. Shake frequently and vigorously 3 g. of the root in powder with 60 g. of ether and 2.5 ml. of dilute ammonia, for 30 minutes. Pour the supernatant ethereal liquid through cotton wool, evaporate off the ether completely and repeat with a second portion of 5 ml. of ether. Dissolve the residue in 1 ml. of alcohol, add 5 ml. of N/10 hydrochloric acid, 10 drops of methyl red and heat on a water-bath for one minute; dilute with 20 ml. of recently boiled and cooled water and titrate the excess of acid with N/10 sodium hydroxide: each millilitre of N/10 HCl is equivalent to 0.0238 g. of ether-soluble alkaloid.

Historical. The Brazilian root was first brought to Europe in 1648 by Piso. It was subsequently given for dysentery, chiefly in small doses, by several Anglo-Indian physicians. In 1858, E. S. Docker, I.M.S., introduced large doses (60 grains two or three times daily) for severe dysentery in Mauritius. G. F. pointed out that we are indebted to Dr. J. L. Bardsley, of Manchester (1821) for the empirical use of emetine in dysentery.

Paul and Cownley stated the average composition of Rio and Carthage alkaloids to be: emetine in Rio 72%, in Carthage 40.5%; cephaeline in Rio 25.9%, Carthage 56.8%. See also H. R. Jensen, *Pharm. J.*, i/1916, 519.

In the initial maceration of the *B.P.* assay process the powdered drug should be shaken with the ether-chloroform mixture for at least 15 minutes, otherwise percolation to complete extraction is very prolonged.—P. A. W. Self, *Pharm. J.*, i/1933, 244.

Of 37 samples, only 7 failed to comply with *B.P.* requirements for alkaloids. The average content of total alkaloids was 2.31%, and of non-phenolic alkaloids calculated as emetine, was 1.59%.—C. E. Corfield, *Yearb. Pharm.*, 1934, 6.

Ipecacuanha Pulverata (*B.P.* '32). Adjusted to contain 1.9% to 2.1% total alkaloids of ipecacuanha, calculated as emetine, not less than two-thirds being non-phenolic alkaloids, calculated as emetine. Ash, not more than 5.5%.

Extractum Ipecacuanhæ Liquidum (*B.P.* '32). Contains 1.9% to 2.1%

total alkaloids of ipecacuanha, calculated as emetine. Assayed by extraction in an acid liquid, made ammoniacal, with chloroform, evaporation and titration the alkaloid. Alcohol content, 75% to 80% *v/v* of ethyl alcohol. Fluid-extractum Ipecacuanhæ, *U.S.P. X*, yields 1.35% to 1.65% *w/v* of ether-soluble alkaloids of ipecac.

The alteration in the *B.P.* assay process has increased the strength by an amount variously estimated as from 10% to 17%.—P. A. W. Self, *Pharm. J.*, 1933, 244.

Tinctura Ipecacuanhæ (*B.P.* '32). Contains 0.095% to 0.105% *w/v* of total alkaloids of ipecacuanha, calculated as emetine. Alcohol content, 20% to 80% *v/v* of ethyl alcohol. Assayed by cleansing of an acid mixture with chloroform, followed by ammoniacal chloroform extraction. Tinctura Ipecacuanhæ, *F.V.*, yields 0.135% to 0.165% *w/v* of ether-soluble alkaloids of ipecac. Tinctura Ipecacuanhæ I.A. contains 0.2% of total alkaloids and is prepared with 70% alcohol.

Emetina (*B.P.C.* '34). $C_{29}H_{40}O_4N_2 = 480.3$. Loss on drying in a vacuum at atmospheric temperature, not more than 1%. Ash, not more than 0.1%. Complies with the limit test for cephaeline.

Emetinæ Hydrochloridum (*B.P.* '32). $C_{29}H_{40}O_4N_2 \cdot 2HCl \cdot 7H_2O = 679.4$. Loss at 100°, 15% to 19%. Ash, not more than 0.1%. By extracting emetine with chloroform, from a solution made alkaline with sodium hydroxide, acidifying the aqueous liquid, adding ammonia, extracting with chloroform and drying at 100°, a limit of cephaeline equivalent to not more than 2% of the alkaloid is included. Emetinæ Hydrochloridum, *U.S.P. X*, should lose not more than 19% at 100°. The same limit of cephaeline, but extracted with ether, allowed.

Emetinæ et Bismuthi Iodidum (*B.P.* '32). Contains 25% to 28% of emetine, $C_{29}H_{40}O_4N_2$, and 18% to 21% of Bi. Loss at 100°, not more than 2%. Assayed for emetine by titration, with N/10 sulphuric acid, of the alkaloid extracted with chloroform from an acid mixture made ammoniacal; and for bismuth by precipitation with ammonium phosphate from the ammoniacal liquids just neutralised with hydrochloric acid, finally weighing the ignited residue.

ISPAGHULA

Ispaghula (*B.P.C.* '34). Foreign organic matter, not more than 3%. Weight of 100 seeds, 0.17 g. to 0.22 g. Agitated in a 25 ml. stoppered cylinder with 20 ml. of water occasionally during 24 hours and allowed to stand for one hour, 1 g. occupies not less than 10 ml.

Psyllium (*B.P.C.* '34). Foreign organic matter, not more than 3%. Weight of 100 seeds, 0.09 g. to 0.13 g. 1 g. agitated with water, as described under Ispaghula, occupies not less than 12 ml.

Ispaghula and Psyllium of Commerce. All the seeds present in commercial samples of Ispaghula examined are seeds of *P. ovata*. Seed of *P. simplexicaulis* appears to be unobtainable commercially. Commercial samples of "Psyllium" seed sometimes consist of seeds of either *P. arenaria* or *P. lanceolata*, partly or wholly. "Bartung" or "Barhang" consists of seeds of *P. major*. It does not occur as an article of commerce in European countries though used widely in the East.—E. W. Skyrme, *Quart. J. Pharm.*, 1935, 11.

JABORANDI

Jaborandi, (*B.P.C.* '34). Consists of the dried leaflets of *Melicope microphyllus* Stapf, and contains not more than 5% of stalks, stems and other foreign organic matter.

P. microphyllus is largely used in making pilocarpine and was official in *U.S.P. IX* if yielding not less than 0.6% of alkaloids.

Pilocarpinæ Hydrochloridum (*B.P.C.* '34). $C_{11}H_{16}O_2N_2 \cdot HCl = 244.6$. M.p., 204° to 205°, after drying to constant weight at 100°. Specific rotation determined on a 10% *w/v* aqueous solution, +90° to +92°. Ash, not more than 0.1%. Complies with tests for foreign alkaloids. The *U.S.P. X* requires the ash from 0.1 g. to be negligible, and the tests for foreign alkaloids by the absence of turbidity with ammonia and with potassium dichromate are also included.

Pilocarpinæ Nitras (*B.P.* '32). $C_{11}H_{16}O_2N_2 \cdot HNO_3 = 271.2$. M.p., 174 to 178°. Specific rotation of the 10% *w/v* aqueous solution, +77° to +83°. Ash, not more than 0.1%. Complies with tests for certain other alkaloids. The *U.S.P. X* requires the ash from 0.1 g. to be negligible, and the salt must comply with tests for various foreign alkaloids.

JALAPA AND IPOMŒA

Jalapa (*B.P.* '32). Should contain not more than 2% of foreign organic matter, and not less than 9% of resin. Assayed by the *B.P.* method by continuous extraction of 20 g. with 90% alcohol, evaporation of the solvent, washing of the residue with four quantities of 10 ml. of hot water, and drying at 100°. Jalapa *U.S.P. X*, should yield not less than 7% of total resins of jalapa assayed by digesting on a water-bath for 3 hours with alcohol followed by percolation and adjusting the percolate to volume by shaking an aliquot part with chloroform and saturated potassium citrate solution, standing overnight, evaporating the alcohol, the chloroform and drying at 100°.

Tubera Jalapæ, *P.G. VI*, contains not less than 10% of resin. Tuber Jalapæ, *P. Helv. V*, contains not less than 10% of resin which should yield not more than 3% to ether.

Jalapa Pulverata (*B.P.* '32). Adjusted with powdered exhausted jalapa or with lactose to contain 9% to 11% of resin.

Jalapæ Resina (*B.P.C.* '34). The dried substance contains not less than 85% of ether-insoluble resins. Loss at 100°, not more than 5%. Ash, not more than 0.5%. Water-soluble matter, not more than 2%. Assayed by shaking vigorously with 50 parts of freshly distilled ether, standing and evaporating, and drying at 100° the decanted ether and washings. Resina Jalapæ, *U.S.P. X*, should yield not more than 30% of chloroform-soluble matter, dried at 100° and not more than 12% of ether-soluble resins; loss at 100°, not more than 1%. Resina Jalapæ, *P. Helv. V*, yields not more than 3% to ether when 1 g. in powder is shaken frequently during 6 hours with 10 g. of ether.

Ipomœa (*B.P.* '32). Ipomœa or Orizaba jalap root (Mexican scammony root) is the dried root of *Ipomœa orizabensis* (Pellet.) Levanis. The resin extracted with 90% alcohol and washed has the properties of Scammonia Resina.

Ipomœa, *U.S.P. X*, yields not less than 15% of total resins by the extraction method with alcohol-chloroform used for Jalapa, *U.S.P. X*; acid-insoluble ash not more than 3%.

Scammonia Resina (*B.P.* '32). Loss at 100°, not more than 5%. Ash, not more than 0.5%. Water-soluble matter, not more than 1%. Contains not more than 40% of ether-insoluble resins, and the ether-soluble resins have an acid value not exceeding 30. Resina Ipomœæ, *U.S.P. X*, leaves not more than 0.5% of ash, and loses not more than 1% at 100°; acid number, 25 to 30; ester number, 170 to 185; saponification value, 195 to 215.

Radix Scammonia, *P. Helv. V*, is described as the dry root of *Convolvulus Scammonia* L., containing not less than 18% of resin; neither scammony nor ipomœa resin is official.

KINO

Kino (*B.P.C.* '34). Extractive to boiling water, not less than 5%. Ash, not more than 2.5%. The *U.S.P. X* requires Kino to yield not less than 45% of alcohol-soluble extractive and not less than 80% of water-soluble extractive.

Kino Eucalypti (*B.P.C.* '34) Alcohol (90%) extractive, not less than 80%. Ash, not more than 3%. The *N.F.V.* does not specify standards for Eucalypti Gummi.

LECITHINUM

Lecithin is a mono-aminophosphatide. Phosphatides are complex bodies of more or less fatty nature which can be extracted from tissues by alcohol, ether, etc., and which contain fatty acids, nitrogen and phosphorus. They are of unstable composition.

On hydrolysis lecithin yields stearic acid, glycerophosphoric acid and choline.

Lecithins may be derivatives of either stearic, palmitic, or oleic acid, alone or mixed. Ovolecithin is generally assumed to be mainly stearyl, i.e., **cholelistearylglycerophosphate**, and plant lecithin to be mainly an oleic acid body, but the fatty acids are not determined with certainty.

Lecithin Content of Various Substances in percentages—

Brain	16.0	Egg Yolk	12.0
Heart	4.5	Peas	1.2
Liver	4.3	Lupin Seeds	2.0
Kidneys	8.5	Ergot	1.7
Lung	1.5	Yeast (dry)	2.0
Spinal Cord	11.0	Barley	0.7
Nerve Tissue (dry)	17.0	Wheat and Rye	0.6
Blood Corpuscles	0.46	Green Peas	0.15
Mushrooms	0.9		

Ovolecithinum (*B.P.C.* '34) is the lecithin prepared from dried egg-yolk and is required to contain 3.5% of phosphorus.

If the cadmium compound of "lecithin" is recrystallised from a mixture of ethyl acetate and 80% alcohol the true lecithin can be freed from kephalin and then liberated from its cadmium compound by means of ammonium carbonate.

Determination of Lecithin in Preparations. Extract 1 g. to 2 g. of a lecithin preparation, or 5 g. to 20 g. of a food stated to contain it, with 96% alcohol—first in the cold and then twice under a reflux condenser. Then extract the insoluble portion with boiling chloroform 2 hours. The combined alcohol and chloroform extractives are evaporated and the residues are digested for 2 hours with 100 ml. of chloroform to separate the lecithin from phosphoric acid, glycerophosphoric acid, etc. To estimate phosphorus pentoxide in the purified extractive, incinerate and oxidise with sulphuric and nitric acids or ignite with magnesium oxide, and bring to weight as pyrophosphate in the usual manner. The factor 11.36 is used to convert the amount found of P_2O_5 into lecithin.

Lipoids are an essential in the food of animals. Among the lipoids there is a series of definite phosphatides, of which the molecule consists of glycerophosphoric acid and a fat acid with a nitrogenous base. Each organ of the body elaborates one or more specific lipoids. Organs or glands which are insufficient or impaired are found to lack lipoids, their power to elaborate them from the materials of the blood being diminished.

LIGAMENTA

Ligamentum Crispi (*B.P.C.* '34). Crêpe bandage when fully extended should measure not less than twice the length of the unstretched bandage; after being fully extended for one minute, it returns to not more than two-thirds the fully extended length.

Contains not less than 33·3% of wool, all in the warp. A 3-inch bandage contains in the warp not less than 47 cotton threads and 94 wool threads with 2 two-fold binding threads at each edge. There are one two-fold cotton thread (right twist), 2 wool threads, one two-fold cotton thread (reverse twist), 2 wool threads, in the warp threads. Count of the wool, not coarser than 25's and not finer than 30's (worsted count). The warp threads are made of two-fold cotton yarn with a finished count, after doubling, not finer than two-fold 20's and containing not fewer than 54 folded turns per inch. Weft should consist of 20's count cotton threads numbering not less than 25 per inch when fully stretched. Weight of 3 inch wide fully stretched bandage, not less than 617 grains per 5 yards.

Ligamentum Domettæ (*B.P.C.* '34). Domette bandage contains not less than 66·6% of wool. Foreign matter, not more than 2%; weight of 2 inch by 6 yards bandage, not less than 440 gr. Minimum average number of threads per inch, 40 in the warp and 22 in the weft, and the total number per sq. inch, 65.

Ligamentum Elasticum Adhesivum (*B.P.C.* '34). A fully stretched elastic adhesive bandage of 3 inches by 5 yards contains not less than 2 oz. of rubber adhesive compound, and after removal of this and other foreign matter and correcting for natural moisture regain, weighs not less than 1·75 oz. When released the fully stretched bandage returns to not more than 80% of its length. Warp threads not less than 44 per inch and made of two-fold cotton yarn with a finished count, after doubling, not finer than two-fold 26's and containing not fewer than 44 folded turns per inch, and woven 2 ends right twist and 2 ends reverse twist. Weft threads not less than 20 per inch when fully stretched, and of cotton yarn not finer than 8·5's.

Ligamentum Lanulæ (*B.P.C.* '34). Flannel bandage must contain not more than 3% of foreign matter. Weight, not less than 900 gr. per 2 inches by 6 yards. Minimum average threads per inch, 26 in the warp and 28 in the weft.

Ligamentum Linæ (*B.P.C.* '34). Bleached calico bandage contains not more than 1·5% of foreign matter. Weight, not less than 210 gr. per 2 inches by 4 yards. Minimum average threads per inch, 67 in the warp and 58 in the weft.

Ligamentum Linæ Crudæ (*B.P.C.* '34). Unbleached calico bandage contains not more than 10% of foreign matter. Weight, not less than 250 gr. per 2 inches by 4 yards. Minimum average threads per inch, 65 in the warp and 60 in the weft.

Ligamentum Pastæ Zinci (*B.P.C.* '34). The warp of zinc paste bandage should be of cotton yarn of a count not finer than 40's and not heavier than 30's and from 30 to 35 threads per inch; the weft, of cotton yarn, 26's to 16's and 20 to 25 threads per inch.

Ligamentum Sindonis (*B.P.C.* '34). Muslin bandage contains not more than 1·5% of foreign matter. Weight per 2·5 inches by 6 yards, not less than 190 gr. Minimum average threads per inch, 48 in the warp and 30 in the weft.

Ligamentum Textum Apertum (*B.P.C.* '34). Open-weave bandage contains not more than 1·5% of foreign matter. Weight per 2 inches by 4 yards not less than 200 gr. Minimum average threads per inch, 43 in the warp and 27 in the weft. Bleached count of the warp yarn, 40's to 33's.

LINUM

Linum (*B.P.* '32). Should contain not more than 2% of foreign organic matter. Linum, *U.S.P. X*, contains not more than 2% of other seeds or foreign organic matter. Non-volatile ether-soluble extractive, not less than 30%, at least 98% of which is saponifiable.

Linum Contusum (*B.P.* '32). Ash, not more than 5%. Should yield not less than 30% of fixed oil having the characters and properties of *Oleum Linum* *B.P.* '32, when continuously extracted with ether.

LIQUOR FORMALDEHYDI

Liquor Formaldehydi (*B.P.* '32). Contains 37% to 41% *w/v* of CH_2O . Sp. gr., 1.080 to 1.095. Estimated by the formic acid formed on warming on a water-bath with hydrogen peroxide and N/1 sodium hydroxide and back titration of the excess alkali with N/1 sulphuric acid to phenolphthalein, a blank titration being performed. Liquor Formaldehydi, *U.S.P. X*, should contain not less than 37% *w/v* of $\text{H}\cdot\text{CHO}$.

Formaldehyd solutus, *P.G. VI*, should contain at least 35% of $\text{H}\cdot\text{CHO}$, determined by the following method:—About 1 g. of solution, accurately weighed, is placed in 100 ml. flask containing 5 ml. of water and 2.5 ml. of N/1 potassium hydroxide. After shaking, make up to 100 ml. 10 ml. of the solution is now mixed with 50 ml. of N/10 iodine and 20 ml. of N/1 potassium hydroxide added. After 15 minutes, add 10 ml. of dilute sulphuric acid, and titrate with N/10 sodium thiosulphate.

For every 0.1 g. of formaldehyde solution, at least 23.3 ml. of N/10 iodine is required, so that for the saturation of the excess iodine at most 26.7 ml. of N/10 sodium thiosulphate is necessary. This represents a content of at least 35% formaldehyde (1 ml. of N/10 iodine = 0.001501 g. of formaldehyde, using starch as indicator).

Formaldehydum solutum, *P. Helv. V*, should contain 35% to 36.5% of $\text{H}\cdot\text{CHO}$ and is assayed as follows:—Dilute about 6 g. with water to 100 ml.; to 25 ml. add 3 drops of thymolphthalein and neutralise with N/1 sodium hydroxide to produce a blue colour. Add a freshly prepared solution of 6.5 g. of solid sodium sulphite in 25 ml. of water made neutral to thymolphthalein with N/1 sodium hydroxide, shake gently and titrate with N/1 hydrochloric acid until the solution is completely decolorised. Each millilitre of N/1 HCl is equivalent to 0.03002 g. of $\text{H}\cdot\text{CHO}$.

The specification of the Association of British Insecticide Manufacturers (Bulletin No. 82: Ministry of Agriculture and Fisheries) requires Liq. Formaldehyde to be a colourless solution, neutral or faintly acid, containing not less than 36% nor more than 40% *w/v* formaldehyde.

Formaldehyde and acetaldehyde can be distinguished and determined, when mixed, with dimedone (dimethyldihydroresorcinol).—M. V. Jonescu and H. Slusanschi, *Bull. Soc. Chim.*, 1933, 53, 909.

The addition of formaldehyde to milk is prohibited by the Public Health (Milk and Cream) Regulations 1922, and by the Public Health (Preservatives in Food) Regulations 1925, *vide Milk Analysis*.

Formaldehyde is an important raw material in the artificial silk industry and in the varnish and lacquer trades.—Report of the Department of Scientific and Industrial Research on "The Production of Formaldehyde by Oxidation of Hydrocarbons" (*Chemistry Research, Spec. Rep.*, No. 1, H.M.S.O., 1927; *Chem. & Drugg.*, i/1928, 382).

Determination of Formaldehyde in Tablets. A colorimetric method of estimating formaldehyde and paraformaldehyde in tablets, using Schiff's reagent. The results obtained from commercial samples varied from 0.021 g. to 0.002 g. in commercial formaldehyde and menthol tablets weighing 0.791 g. and 0.69 g. respectively. An average content appears to be about 0.01 g.—N. Evers and C. M. Caines, *Yearb. Pharm.*, 1921, 321.

Poisoning from taking 300 g. of 40% formaldehyde. Death in 6 hours.—*Pharm. J.*, i/1924, 555.

Production of Formaldehyde by Intestinal Bacteria. Schryver's test the most delicate and reliable: to 10 ml. of suspected solution add 2 ml. of 1% solution of phenylhydrazine hydrochloride, then 1 ml. of 5% potassium ferricyanide solution, and then 2 ml. of concentrated hydrochloric acid—a pink colour appears if formaldehyde is present (this colour soon fades, but is brought back and intensified, by hydrogen peroxide). Table showing results of tests applied to various organisms. Test should be of considerable value in classification and identification of bacteria.—B. H. Shaw, *Brit. med. J.*, i/1924, 461.

Paraformaldehydum (*B.P.C.* '34). By the oxidation method used for Liquor Formaldehydi, it contains not less than 95% of $(\text{CH}_2\text{O})_3$. Ash, not more than 0.1%. The *U.S.P. X* also requires a purity of 95%.

Paraldehydum (*B.P.* '32). Sp. gr., 0.998 to 1.000. Distillation range, not more than 10% below 123° , the remainder between 123° and 126° . M.p., not below 11° . Complies with limit tests for acidity, acetaldehyde and peroxidised compounds. Paraldehydum, *U.S.P. X*, should comply with purity tests for impurities derived from fusel oil, amyl alcohol, sulphate, chloride, free acid and acetaldehyde.

LIQUOR HYDROGENII PEROXIDI

Liquor Hydrogenii Peroxidi (*B.P.* '32). Contains 2.5% to 3.5% *w/v* of H_2O_2 , corresponding to about ten times its volume of available oxygen. Residue on evaporation on a water-bath not more than 0.2% *w/v*. Complies with limit tests for barium and acidity. Assayed by titration with potassium permanganate. Liquor Hydrogenii Dioxidum, *U.S.P. X*, contains not less than 3% by weight of H_2O_2 .

P.G. VI gives method of estimation by titrating iodine liberated from potassium iodide.

Preservatives.

BENZOIC ACID 0.05% added to hydrogen peroxide solution is said to be a good preservative.

ACETANILIDE 0.002% with hydrochloric acid 0.02%, or with phosphoric acid 0.1%, will keep 10 vol. hydrogen peroxide for several weeks. The first combination was best of the series, but the loss in strength is nevertheless grave. The loss after keeping 4 years amounted to 70% to 99%.—H. R. Jensen, *B.P. Conf.* 1920.

PHENACETIN, 0.1%, has been found more effective than acetanilide as a stabiliser.

ETHYL ALCOHOL added in proportion of 10% by volume has been suggested.

LOBELIA

Lobelia (*B.P.* '32). Contains not more than 60% of stems and not more than 2% of foreign organic matter. Acid-insoluble ash not more than 5%. Lobelia, *U.S.P. X*, should contain not more than 10% of stems and 2% of other foreign organic matter, and should leave not more than 5% of acid-insoluble ash. *Herba Lobeliæ*, *P. Helv. V*, when assayed by the process prescribed yields not less than 3% of alkaloids; ash, not more than 13%.

Lobelinum hydrochloridum, $\text{C}_{22}\text{H}_{27}\text{O}_2\text{N}\cdot\text{HCl}$, is official in the *P.G. VI*. Lobelinum hydrochloricum, *P. Helv. V*, dried over sulphuric acid, contains not more than 1% of moisture; 0.4 g. in 20 ml. of water at 20° in a 200 mm. tube has an optical rotation of -2.23° to -2.33° ; the separated alkaloid, after drying over sulphuric acid for 24 hours, melts at a temperature not below 116° . Titration with sodium hydroxide to phenolphthalein should show not less than 99.3% of $\text{C}_{22}\text{H}_{27}\text{O}_2\text{N}\cdot\text{HCl}$.

MAGNESIUM

Magnesii Carbonas Levis (*B.P.* '32). Residue on ignition, 2% to 45%. **Magnesii Carbonas**, *U.S.P. X*, by titration with excess of N/1 sulphuric acid and N/1 sodium hydroxide to methyl orange, contains the equivalent of not less than 39.2% of MgO; a calcium limit equivalent to not more than 0.8% is included. **Magnesii Carbonas Ponderosus**, *B.P.* '32, leaves a residue on ignition of 42% to 45%. **Magnesium subcarbonicum**, *P. Helv. V*, yields on ignition from 39.0% to 44.1% of residue and the residue contains not less than 99% of MgO.

Liquor Magnesii Bicarbonatis (*B.P.* '32). Should contain not less than 2.5% w/v of Mg (HCO₃)₂. Assayed by titration of total alkalinity to methyl orange with subtraction of the alkali limit titration obtained by boiling the ignited residue with water, filtering and titrating.

Magnesii Hydroxidum (*B.P.C.* '34). Mg(OH)₂ = 58.34. Residue on ignition, 67% to 70%.

Mistura Magnesii Hydroxidi (*B.P.* '32). Contains the equivalent of 7.75% to 8.75% w/v of Mg(OH)₂. **Magma Magnesiae**, *U.S.P. X*, contains not less than 7% of Mg(OH)₂.

Magnesii Oxidum Leve (*B.P.* '32). MgO = 40.32. Loss on ignition, not more than 5%. **Magnesii Oxidum**, *U.S.P. X*, loses not more than 10% on ignition, and then contains not less than 96% MgO, by titration of alkalinity to methyl orange less the calcium determined as for the carbonate. **Magnesii Oxidum Ponderosum**, *B.P.* '32, loses not more than 5% on ignition. The *U.S.P. X* substance loses not more than 10% on ignition, and then contains not less than 96% of MgO. **Magnesium oxydatum**, *P. Helv. V*, loses not more than 15% of its weight on ignition, and the ignited substance contains not less than 99% of MgO.

Magnesium metal may prove dangerous in certain conditions, e.g., when powdered and mixed with an equal quantity of silver nitrate, and a drop of water added, a slight explosion with flash may occur. With mercuric nitrate there is vigorous reaction; brown fumes rise but there is no flash.

Magnesium and palladious chloride together in certain proportions will cause water to decompose at ordinary temperature.

Magnesia Mixture. Solution of Magnesium Ammonio-Sulphate. Dissolve magnesium sulphate 20, ammonium chloride 40, in water 160, add ammonia solution 84. Allow to deposit in a stoppered bottle before use. Employed for the gravimetric determination of phosphates. Ammonium magnesium phosphate is precipitated and converted by incineration into magnesium pyrophosphate, Mg₂P₂O₇.

MENTHA PIPERITA

Mentha Piperita (*B.P.C.* '34). Should contain not more than 2% of foreign organic matter, and yield not more than 2% of acid-insoluble ash. **Mentha Piperita**, *U.S.P. X*, contains not more than 2% of stems more than 3 mm. in diameter, or other foreign organic matter.

Folia Menthae piperitæ, *P.G. VI*, yields not less than 0.7% of volatile oil.

Oleum Menthae Piperitæ (*B.P.* '32). Contains 4.5% to 9% w/w of esters, calculated as menthyl acetate, C₁₂H₂₂O₂, and not less than 46% w/w of free menthol, C₁₀H₂₀O. Sp. gr., 0.902 to 0.910. α_D, -18° to -32°. n_D^{20°}, 1.460 to 1.470. Soluble in 4 volumes of alcohol (70%, sp. gr. 0.8896 to 0.8901). Assayed for ester content by boiling the neutralised oil with N/2 alcoholic potash for 1 hour and back titrating with N/2 sulphuric acid, and performing a blank; the acetylated oil obtained by boiling gently for 2 hours with acetic anhydride and anhydrous sodium acetate, washing the product and drying over anhydrous

sodium sulphate, is treated as for the ester determination. The free alcohols are calculated from the ester values of the original and acetylated oils using the *B.P.* formula. *Oleum Menthæ Piperitæ*, *U.S.P. X*, contains not less than 5% of esters as menthyl acetate, and not less than 50% of total menthol, free and as esters. Assayed similarly to the *B.P.* process and an equation for calculation is given.

The Food and Drug Administration of the U.S. Dept. of Agriculture define oil of peppermint, for food purposes, as the volatile oil obtained from peppermint (*Mentha piperita* L.), containing not less than 50% by weight of menthol.—*S.R.A., F.D., No. 2, Rev. 4, Aug., 1933.*

English and American oils are distilled from *Mentha piperita*. Two varieties are used, black and white; the former gives the larger yield of oil and is almost exclusively used, but the latter gives an oil of finer quality.

Studies of the genus *Mentha*.—Kremers, *Perfum. essent. Oil Rec.*, 1925, 409, and *ibid.*, 1926, 90.

For identity of aldehydes, ketones, etc., in American oil, also American peppermint distillation, see Bulletin No. 1555, U.S. Dept. of Agriculture, which also gives details of types of plants, soil, cultivation and distillation. Tabulated figures for a large number of oils taken over two seasons are given by Lazell (*Perfum. essent. Oil Rec.*, 1928, 183).

Evaluation of menthone in peppermint oil. Determination as the semicarbazone is compared with the oxime method.—Reilley, Moonan and Drumm, *Perfum. essent. Oil Rec.*, 1931, 378.

Japanese peppermint oil is obtained from *Mentha arvensis*. Undementholised oil contains about 85% of menthol, dementholised oil about 50%; both varieties are commercial oils. Details of the distillation of peppermint oil in Japan are given in *Perfum. essent. Oil Rec.*, 1931, 241. For the constitution of the high boiling fraction of Japanese oil see Shinosaki and Nagasawa, *Perfum. essent. Oil Rec.*, 1931, 172.

The principal terpenes in the oil are limonene and α -pinene, and the sesquiterpene fraction is mostly caryophyllene.—Duncan and Short, *J. Soc. chem. Ind., Lond.*, 1931, 198 T.

Some difficulty has been experienced in obtaining American oils containing the *B.P.* limit for free menthol. Japanese oil, from *Mentha arvensis*, is not *B.P.*, and redistilled Japanese mint oils will no longer conform to *B.P.* tests.—C. T. Bennett, *Pharm. J.*, i/1933, 150.

For details of the production and analytical characters of **Franco-Mitcham** peppermint oil see *Perfum. essent. Oil Rec.*, 1926, 170, and for **Italo-Mitcham** oil see *Pharm. J.*, i/1935, 289.

A peppermint oil from WESTERN AUSTRALIA compared favourably with the best American production and closely resembled English distilled oil.—E. J. Parry, *Perfum. essent. Oil. Rec.*, 1924, 188.

Menthol and Peppermint Oil in Alcohol Solution—Test to Distinguish. When tincture of iodine is added to a solution of peppermint oil, several drops, more or less, may be added before the yellow tint of iodine is perceptible. With a solution of menthol there is no absorption, so the yellow tint is seen at once.

Oleum Menthæ Viridis (*B.P.C.* '34). By the method of the *B.P.* for carvone by digestion with hydroxylamine hydrochloride and titration of the liberated acid with N/1 alcoholic potash to dimethyl yellow, not less than 42% of carvone is indicated. Sp. gr., 0.920 to 0.940. α_D , -34° to -55° . n_{D20° , 1.483 to 1.490. Soluble in three volumes of alcohol (90%, sp. gr. 0.8334 to 0.8340). *Oleum Menthæ Viridis*, *U.S.P. X*, yields by the sodium sulphite absorption not less than 43% by volume of carvone; sp. gr. at 25° , 0.917 to 0.934; α_D at 25° , -38° to -56° ; n_{D20° , 1.4820 to 1.4900.

The *U.S.P. X* minimum standard is lower than the quality of the market product warrants. α_D , -48° to -59° and a minimum carvone content of 50% are justified.—Warren, *Quart. J. Pharm.*, 1933, 595.

Oleum Pulegii (*B.P.C.* '34). Contains not less than 85% *v/v* of pulegone. Sp. gr., 0.930 to 0.960; α_D , $+14^\circ$ to $+28^\circ$; n_{D20° , 1.475 to 1.490. Soluble in three volumes of alcohol (70%, sp. gr. 0.8896 to 0.8901). Assayed by measurement of the oil unabsorbed by sodium sulphite solution and deduction from the original volume.

Menthol (B.P. '32). $C_{10}H_{20}O = 156.2$. M.p., 42° to 43° . Residue on volatilisation, not more than 0.05%. Menthol, U.S.P. X, has a m.p. of 2° to 44° , and complies with tests for wax, paraffin or organic substances, and for thymol.

Menthol from Mexico. The Department of Industry, Commerce and Labour, in Mexico, advises the exploitation of a plant known as tabaquillo, but botanically termed *Hedeoma piperita* Benth., which grows wild in Mexico in large quantities. The use of the name tabaquillo may prove misleading, as there are no less than six plants to which the name is applied in Mexico.

Further investigation of the two plants *Calamintha macrostema* Benth., and *Hedeoma piperita* Benth, both known as tabaquillo, is desirable; although both may contain menthol, the other constituents of the volatile oil present in each may be different.—E. M. Holmes, *Chem. & Drugg.*, ii/1928, 649.

MYRISTICA

Myristica (B.P. '32). Nutmegs should consist only of the dried kernels of *Myristica fragrans*. Myristica, U.S.P. X, yields not less than 25% of non-volatile, ether-soluble extractive and not more than 0.5% of acid-insoluble ash.

The Food and Drug Administration of the U.S. Dept. of Agriculture define nutmeg as the dried seed of *Myristica fragrans* Houtt, deprived of its testa, with or without a coating of lime. Contains not less than 25% of non-volatile ether extract, not more than 10% of crude fibre, not more than 5% of total ash nor more than 0.5% of ash insoluble in hydrochloric acid. Macassar nutmeg, Papua nutmeg, male nutmeg, long nutmeg, is the dried seed of *Myristica argentea* Warb., deprived of its testa.—S.R.A., F.D. No 2, Rev. 4., Aug. 1933.

Oleum Myristicæ (B.P. '32). Sp. gr., 0.880 to 0.925. α_D , $+10^{\circ}$ to $+30^{\circ}$, $n_{D20^{\circ}}$, 1.474 to 1.488. Residue on evaporation in a flat dish on a water-bath, not more than 3%. Soluble in three volumes of alcohol (90%, sp. gr. 0.8334 to 0.8340). The U.S.P. X oil has a sp. gr. at 25° of 0.859 to 0.924; α_D at 25° , $+12^{\circ}$ to $+30^{\circ}$, $n_{D20^{\circ}}$, 1.4780 to 1.4895.

Oleum Myristicæ Deterpenatum (B.P.C. '34). Soluble in three volumes of alcohol (80%, sp. gr. 0.8634 to 0.8640). Sp. gr., 1.040 to 1.100; α_D $+1^{\circ}$ to $+14^{\circ}$; $n_{D20^{\circ}}$, 1.500 to 1.533.

Mace. The Food and Drug Administration of the U.S. Dept. of Agriculture define mace as the dried arillus of *Myristica fragrans* Houtt. Contains not less than 20% nor more than 30% of non-volatile ether extract, not more than 10% of crude fibre, not more than 3% of total ash, and not more than 0.5% of ash insoluble in hydrochloric acid. Macassar mace, Papua mace: the dried arillus of *Myristica argentea* Warb.—S.R.A., F.D., No. 2, Rev. 4, Aug. 1933.

The Nutmeg Industry. The principal sources of supply are the Dutch East Indies and Granada, the former exporting about three times as much as the latter. East Indian nutmegs are "round," i.e., nearly spherical. Granada nutmegs are mixed "round" and "long," i.e., length exceeding diameter by $1\frac{1}{2}$ to 2 times. Granada nutmegs are not inferior but are liable to be confused with the Papuan (New Guinea) false long nutmeg derived from *M. argentea*, which is of inferior quality, but resembles the genuine in external appearance.—*Bull. imp. Inst.*, Lond., 1933, 31, 2, 197.

Oil distilled from nutmegs of *M. argentea* has an odour reminiscent of sassafras.—Gildermeister and Hoffman.

The oil distilled from Granada nutmegs seems to differ from that of E. Indian nutmegs with a tendency to a lower specific gravity.

The oil distilled from mace, although smaller in yield is almost indistinguishable from nutmeg oil.

The nutmegs of commerce.—E. M. Holmes, *Pharm. J.*, i/1909, 419, 459; see also *Chem & Drugg.*, i/1914, 160.

Constitution of oil of nutmeg.—F. B. Power and A. H. Salway, *Trans. chem. Soc.*, 1907, 91, 2037.

NICOTINA

The specification of the Association of British Insecticide Manufacturers (Bulletin No. 82: Ministry of Agriculture and Fisheries) for nicotine requires the material to be free from coal tar bases and the nicotine content to be declared.

Nicotine is a powerful poison when applied to the skin. Collapse of a girl in an insecticide factory following the spilling on her overall sleeve of 2 drachms of 95% solution. Saved by emetics and scrubbing the skin with soap and cold water (hot water accelerates absorption).—L. P. Lockhart, *Brit. med. J.*, i/1933, 247; see also A. M. Aitken, *ibid.*, 341.

Accidental poisoning of an American florist by spilling on the clothes an insecticide containing 40% of free nicotine. Nausea, vomiting, sweating and dyspnoea. Symptoms cleared up in 3 weeks.—J. M. Faulkner, *J. Amer. med. Ass.*, i/1933, 1664.

Insecticides. The Association of British Insecticide Manufacturers have prepared approved specifications with method of analysis, for certain insecticides and fungicides. By requiring such substances to comply with the specifications, purchasers are able to obtain standard products of high quality.

The products include lead arsenate in powder or paste, lime-sulphur solution, nicotine and nicotine sulphate, copper sulphate, burgundy powder, cheshunt compound, soft soaps for spraying, sodium, potassium and calcium cyanides, and formaldehyde.—Bulletin No. 82, 1934, Ministry of Agriculture and Fisheries.

NUX VOMICA

Nux Vomica (*B.P.* '32). Contains not less than 1·2% of strychnine and not more than 1% of foreign organic matter. Assayed by continuous extraction with a mixture of alcohol, dilute solution of ammonia and chloroform (12 : 1 : 4), followed by evaporation of the solvent and extraction with sulphuric acid from a chloroform mixture; the total alkaloids are then extracted with chloroform from ammoniacal solution, the solvent evaporated, alcohol added, and evaporated; the residue is dissolved in 15 ml. of 3% sulphuric acid and 2 ml. of nitric acid, allowed to stand for 30 minutes at 15° to 20°, made alkaline with sodium hydroxide and extracted with chloroform; the residual strychnine, after drying for 30 minutes at 100°, is titrated with N/10 sulphuric acid to methyl red or cochineal.

Nux Vomica, *U.S.P. X*, contains not less than 2·5% of total alkaloids of *Nux Vomica*; assayed by the aliquot part method macerating with ether-chloroform and finally extracting with chloroform and estimating the alkaloid volumetrically. *Semen Strychni*, *P.G. VI*, contains not less than 2·5% of total alkaloids of *Strychnos nux vomica* Linné. *Semen Strychni*, *P. Helv. V*, contains not less than 2·5% of total alkaloid and the powder for administration is adjusted with lactose to contain 2·5% of total alkaloid.

Strychnos cinnamomifolia from Travancore. Total alkaloidal content from 2·432% to 2·801%, only about 0·3% being strychnine. The seeds closely resemble those of *S. Nux-vomica*, but have not been commercially exploited.—G. R. A. Short, *Yearb. Pharm.*, 1924, 646.

Benzol (*B.P.* '98) is not such a good solvent for strychnine as chloroform but is advised, in preference to the latter, if used in larger quantity for extraction in the estimation process: it does not emulsify.—H. Deane, *Pharm. J.*, ii/1924, 96. See also D. B. Dott, *ibid.*, 251.

Almost all the details of the *B.P.* '14 assay process have been altered, since it contained about five separate serious sources of error.—P. A. W. Self, *Pharm. J.*, /1933, 244.

Toxicology. It is useful to extract with acetic acid and alcohol. The alcohol assists filtration.

Nux Vomica Pulverata (*B.P.* '32). Adjusted with nux vomica of higher or lower alkaloidal content, or with lactose, to contain 1·14% to 1·26% of strychnine. Ash, not more than 3%.

Strychnina (*B.P.C.* '34). $C_{21}H_{22}O_2N_2 = 334\cdot2$. By titration in excess N/10 sulphuric acid with N/10 sodium hydroxide to cochineal, a purity of not less than 99% should be indicated. Ash, not more than 0·1%. A limit test for brucine is included; no reddish colour should be produced with a mixture of equal parts of nitric acid and water. Strychnine, *N.F. V*, should leave not more than 0·1% of ash.

Spectrum of Strychnine. The smallest quantity, e.g., 1/500 grain, can be detected—useful in cases of poisoning. Alkaloids generally give characteristic spectra.—Prof. J. J. Dobbie.

Strychninæ Hydrochloridum (*B.P.* '32). $C_{21}H_{22}O_2N_2\cdot HCl, 2H_2O = 406\cdot7$. Should lose not less than 7% and not more than 9% at 110°. Ash, not more than 0·1%.

Volumetric estimation of Liq. Strychninæ, using N/10 potassium dichromate, which precipitates the alkaloid quantitatively from slightly acid solution.—J. Rae, *Pharm. J.*, i/1928, 270.

Strychninæ Nitras (*B.P.C.* '34). $C_{21}H_{22}O_2N_2\cdot HNO_3 = 397\cdot2$. Ash, not more than 0·1%. Complies with limit tests for brucine and sulphate. The *U.S.P. X* salt should leave not more than 0·1% of ash and comply with tests for acidity, readily carbonisable substances, brucine, chloride and sulphate.

Strychninum nitricum is the only form of strychnine official in the *P. Helv V*. When titrated with N/10 sodium hydroxide using phenolphthalein as indicator, it should contain not less than 99·5% of $C_{21}H_{22}O_2N_2\cdot HNO_3$.

Strychninæ Sulphas (*B.P.C.* '34). $(C_{21}H_{22}O_2N_2)_2\cdot H_2SO_4, 5H_2O = 856\cdot5$. Loss at 100°, 9% to 11%. Ash limit, 0·1%. Complies with the limit test for brucine. Strychninæ Sulphas, *U.S.P. X*, leaves not more than 0·1% of ash and complies with tests for acidity, readily carbonisable substances and brucine.

Quantitative methods for the determination of quinine and strychnine in tablets are described in *Methods of Analysis (A.O.A.C., 1930, 472)*.

ŒSTRINUM

The generic term œstrin is given to the hormones present in the ovaries and certain other tissues of animals. They are identified by their power to transform the vaginal epithelium of ovariectomised rats or mice from the diœstrus to the œstrus form. Human pregnancy urine contains 3-hydroxy-17-keto-1 : 3 : 5-œstratriene, $C_{18}H_{22}O_2$, known as œstrone, ketohydroxyœstrin, or the follicular hormone, and 3 : 16 : 17-trihydroxy-1 : 3 : 5-œstratriene, $C_{18}H_{24}O_3$, called œstriol, trihydroxyœstrin, or the follicular hormone hydrate. A useful general account of the properties of these compounds is given in the *B.P.C.* '34, p. 676 *et seq.*

Œstrone

The standard preparation is the international standard which is a quantity of crystalline ketohydroxyœstrin kept in the National Institute for Medical Research, London. The unit is the amount of activity in 0·0001 mg. of the standard preparation.

Biological Test. The biological test is made on mice or rats from which the ovaries have been removed. The removal of the ovaries is accomplished by making lumbar incisions in the anæsthetised animal. The ovary, together with

adjacent fat, is drawn through the corresponding incision, a silk ligature is tied around the horn of the uterus and the ovary is cut off. The changes in the vaginal epithelium characteristic of the œstrous cycle then are arrested.

If a drop of water be placed in the vagina of a normal rat or mouse, and then withdrawn and examined microscopically, various cells are seen. When the rat is not on heat, during diœstrus, large numbers of leucocytes are seen. When the rat is on heat, in œstrus, leucocytes are absent and the cells are predominantly large non-nucleated squamous cells. Œstrus recurs every 4 or 5 days. In the ovariectomised rat the vaginal cells are chiefly leucocytes, and there is no cycle of changes. If œstrone is injected in sufficient amount the leucocytes disappear and the squamous cells take their place about 48 hours later.

When an unknown preparation is to be tested many rats or mice must be used, as there is a great variation in the response of individuals. At least twenty should be injected with a given dose of the standard, and twenty others with a given dose of the unknown preparation. The percentage in each group which pass through œstrus can then be determined, and the relative potency of the unknown and the standard is calculated by means of a curve (Coward and Burn, *J. Physiol.*, 1927, 63, 270) relating dose to percentage response.

Œstrone is sold in aqueous solution and as a solution in oil. Preparations in aqueous solution must be compared with the standard aqueous solution. The dose is then administered to rats or mice in at least three injections given at intervals of not less than 8 hours. Preparations in solution in oil must be tested in comparison with a solution of the standard in oil. The dose is then given as a single injection. It has recently been shown (Kaufmann, *Proc. R. Soc. Med.*, 1934, May, 849) that the doses necessary for therapeutic use in amenorrhœa are much greater than was formerly supposed, being from 100,000 to 1,000,000 units. These doses cannot be given in aqueous solution as the solubility is too low; they must be injected in solution in oil.

Œstrus-producing hormones.—E. C. Dodds, *Brit. med. J.*, ii/1934, 1187.

The amount of œstrin excreted in the urine of cows during pregnancy is less than 50 international units per litre during the first 21 weeks of gestation. Œstrin can be readily detected in the urine at the 23rd week, when the concentration is about 100 units per litre. At the 30th week 700 units were obtained, and at the 37th, 17,000 units per litre.—M. M. O. Barrie, J. B. E. Patterson and S. W. F. Underhill, *Quart. J. Pharm.*, 1935, No. 3.

Progestin

Progestin is a hormone secreted by the corpus luteum, and is so called because it has the property of bringing about that proliferation of the wall of the uterus which takes place at the beginning of gestation, and which is known as progestational proliferation. It can be estimated in extracts of corpus luteum most readily on the immature rabbit, by administering doses of œstrone to produce initial development of the uterus, and then by injecting the extract of the corpus luteum. If this extract is active it causes the appearance of glands in the epithelial lining of the lumen of the uterus which are at first quite short and do not affect the deeper stroma. Further development results in the glands extending and penetrating deeper, though they are still narrow. Finally, the glands penetrate nearly to the myometrium, and they become distended. The details of the estimation described by McPhail (*J. Physiol.*, 1934, 83, 145) are that rabbits weighing about 900 g. receive a total of 150 international units of œstrone during six days in three equal doses on alternate days. The injections are in solution in oil and made into the muscles of the hind leg. The progestin is then injected in oily solution for 5 days, at the end of which the rabbits are killed and cross sections of the uterus taken for histological examination. The degree of proliferation produced is then assessed numerically by comparison with a scale, and the average figure determined for a group of animals. The unit is the amount of extract required to produce a medium degree of proliferation.

Testicular hormone. Testicular hormone, also spoken of as the male hormone, is available in oily solution as Provironal and Hombreol. It has recently been synthesised, the product being known as androsterone.

Biological Tests. There are two methods of determining the potency, by its effect in producing growth of the cock's comb, and also by its effect in producing growth of the prostate and seminal vesicles of the rat.

The *cock's comb test* is carried out on white leghorns which have been

strated (capons). In such birds the comb regresses to a very small size. Injection of the extract into the breast muscles leads to growth of the comb, the growth being proportional to the dose administered. Usually doses are given daily for 5 days. The growth of the comb is usually measured by taking ahouette photograph and measuring the area of the comb on the photograph by means of a planimeter. The potency of some preparations is expressed in cock's comb units per millilitre, but this unit has no constant value.

The **test on the rat** is performed by castrating male rats not more than 30 days old. They are left for 30 days during which time the prostate and seminal vesicles decrease in size until they reach a steady weight. The rats are then injected daily for 7 days, when they are killed and the prostate and seminal vesicles are dissected and fixed in Bouin's solution. After 24 hours they are dried in blotting paper and weighed. When the weight is calculated per 100 g. body weight of rat, the percentage increase in weight over that of uninjected control animals is proportional to the dose injected. Hence the relative potency of two extracts can be determined by injecting the same dose of each into two groups of rats and determining the average increase in weight produced by each.

It is probable that the crystalline hormone, androsterone, will be adopted as the international standard, and a unit defined as the activity present in a given weight of it.

OLEA ESSENTIALIA

The essential oils and natural perfumes are obtained by distillation, solvent extraction and cold and hot enfleurage processes. **Distillation** yields a true volatile oil but is not suitable where the yield of oil is very small or the product is damaged by heat. The principles of the distillation of essential oils are described in "A Treatise on Distillation," by Durrans (*Perfum. essent. Oil Rec.*, 1920, 154). **Solvent extraction** has largely displaced the enfleurage process for many perfumes, benzene and petroleum ether being used as solvents. The product obtained by the evaporation of the solvent contains, besides the odorous bodies, resins, waxes and colouring matter; these are separated more or less completely by treating the extract with alcohol, refrigerating, filtering and evaporating the alcohol to obtain "*absolutes*." Many perfumes are made by this process, of which the more usual are, jasmine, orange-flower, carnation, violet, lilac, rose, cassie, and oak moss. **The enfleurage process**, in which the odour of the flowers is taken up by repeatedly spreading fresh flowers on trays coated with fat, or by immersing them in melted fat, is still used for jonquil, jasmine, tuberose and a few others. The fat when sufficiently saturated, is extracted with alcohol which is evaporated to leave the "*absolute*." Some account of the process is given in *Chem. & Drugg.*, i/1927, 319.

For further information as to sources, constituents, methods of distillation, yields, analytical and physical data, etc., see *Die Ätherischen Öle*, by Gildermeister and Hoffman; *Chemistry of Essential Oils and Artificial Perfumes*, by E. J. Parry; *Essential Oils*, by H. Finckmore; also Umney, *Perfum. essent. Oil Rec.*, July, 1912; and Bovill, *Mfg Chem.*, Jan.-Feb., 1932. For the chemistry of the terpenes, see Durrans, *Perfum. essent. Oil Rec.*, 1929, 278, also L. Ruzicka, *ibid.*, 1934, 85 and 117.

Determination of Aldehydes. The following method is recommended by the Essential Oil Sub-Committee of the Committee on Uniformity of Analytical Methods for the determination of aldehydes in oils of cassia, cinnamon, lemon-grass, orange, bitter almond, cherry-laurel, cummin and terpeneless oils of lemon

and orange:—Weigh out exactly, into a glass-stoppered tube approximately 150 mm. long and 25 mm. in diameter, a suitable quantity of the oil, add 5 ml. of benzene and 15 ml. of N/2 hydroxylamine hydrochloride reagent; shake vigorously and titrate with N/2 alcoholic potash (60% alcohol) until the red colour changes to yellow; continue the shaking and titrating until the full yellow colour of the indicator is permanent in the lower layer after shaking vigorously for 2 minutes and then allowing to stand for the liquids to separate. The report should be consulted for further details and for the different factors employed.—*Analyst*, 1934, 105.

Micro-Chemistry in the Domain of Essential Oils and Perfumery Materials. Apparatus and methods are described, qualitative tests, and characteristics of materials.—Rosenthaler, *Perfum. essent. Oil Rec.*, 1930, 277.

Estimation of Alcohols in Essential Oils. A method using orthophosphoric acid as a catalyst. Acetylation is completed in about fifteen minutes at ordinary temperatures. The process is not satisfactory for oil of citronella.—Sabatay, *C. R. Acad. Sci., Paris*, 1934, 199, 1419.

Identification of Phenols. Methods given for the identification of thymol, carvacrol, eugenol, iso-eugenol, and vanillin through the melting-points of the arylacetic acids.—Reed, *Perfum. essent. Oil Rec.*, 1933, 190.

The Determination of Solubilities. Report of Sub-Committee on Uniformity of Analytical Methods. The terms used to describe solubility are described.—*Analyst*, 1930, 386. The alcohols used in the solubility tests for volatile oils should comply with the sp. gr. limits—90%, 0.8334 to 0.8340; 80%, 0.8634 to 0.8640; 70%, 0.8896 to 0.8901.

Solubilities of perfumery ingredients, essential oils and synthetics in ethyl alcohol.—*Perfum. essent. Oil Rec.*, 1924, 283.

Essential oils are able to *hold water in solution*, particularly those which contain a large proportion of oxygenated bodies.—see Umney and Bunken, *Perfum. essent. Oil Rec.*, May, 1912.

Determination of Volatile Oil in Drugs. The methods for the determination of essential oils in drugs involve the use of a continuous distillation apparatus in which the drug is distilled in steam and the condensed water, separated from the oil, is returned to the distilling flask, the amount of oil obtained being measured at the end of the operation. Considerable variation has often been found in the yields of oil from different samples of a drug, and it is desirable that minimum limits for the yield of the essential oil in such drugs should be fixed. A method for certain drugs is given in *P.G. VI*. Apparatus and processes have also been described by J. F. Clevenger (*Perfum. essent. Oil Rec.*, 1928, 226), G. R. A. Short (*Quart. J. Pharm.*, 1931, 444), Cocking and Middleton (*ibid.*, 1932, 521, also 1935, No. 3), Kuhn (*Pharm. Ztg.*, 1934, 99, per *Quart. J. Pharm.*, 1934, 691). Further research is desirable in this direction in order to obtain a method for the standardisation of the volatile oil in powdered drugs.

The volatile oil contents of drugs and spices may be determined with apparatus in which the receiver is a standard separating funnel receiver (V. 4) as specified by the Standardisation of Tar-Products Tests Committee. Results are given for a number of substances including nutmeg, cinnamon, clove, caraway, cardamom and umbelliferous fruits.—C. E. Sage and H. R. Fleck, *Analyst*, 1934, 614.

TERPENELESS ESSENTIAL OILS

Essential oils from which the terpenes and sesquiterpenes have been separated by fractional distillation *in vacuo* have the advantage that they are stronger in perfume and flavour and more readily soluble in diluted alcohol than the original oils. Some oils, e.g., clove oil, contain so small a proportion of terpenes that there is generally no point in rendering them terpeneless. In other oils the proportion of the terpenes is so variable that the yield of terpeneless oil differs widely. With the exception of the citrus oils, which are prepared in both the terpeneless and sesquiterpeneless forms, the term terpeneless generally implies an oil which has been obtained by fractionation and is free from both terpenes and sesquiterpenes. The following table is mostly derived from Durrans *Perfum. essent. Oil Rec.*, 1924, 240, with revisions, 1929. In the original article a number of physical data are also given.

Terpeneless and Sesquiterpeneless Oils

	Concen- tration	1 vol. Oil soluble in Alcohol
Absinthe	—	2 to 3 vols. 70%
Angelica	20	3 vols. 70%
Aniseed	1.5	10 vols. 80%
Bay	2—3	1—1.5 vols. 70%
Bergamot	2.5—3	1 vol. 80%; 3—4 vols. 70%
Calamus	—	25 vols. 60%; 3 vols. 70%
Cananga	6	1 vol. 90%
Caraway	2	2 vols. 70%; 19 vols. 50%
Cardamom	2	2—3 vols. 70%
Cassia	2	2 vols. 70%
Cedarwood	—	1 vol. 90%
Celery	8	2 vols. 80%
Cinnamon Leaf	3	1 vol. 70%; 3 vols. 60%
Citronella (Ceylon)	2	2 vols. 70%
Citronella (Java)	1.5	2 vols. 70%
Clove	1.5	2.5 vols. 60%; 1 vol. 70%
Coriander	1.5	2 vols. 70%
Cummin	1.5—2	5—7 vols. 70%
Dill	2—3	2—3 vols. 70%
Eucalyptus Globulus	2—3	2 vols. 70%
Fennel	1.5	1 vol. 90%
Geranium	1.5—2	1—2 vols. 70%
Ginger	12	2—4 vols. 80%
Grape Fruit	50	2 vols. 80%
Hops	8	1 vol. 80%; 20—30 vols. 70%
Juniper Berry	10	1 vol. 90%
Lavender (French)	2	1—2 vols. 70%
Lemon	25	3 vols. 70%
Lemongrass	1.5	2 vols. 70%
Linaloe	1.5	1.5—3 vols. 70%
Limes (Handpressed)	6	2 vols. 70%
Limes (Distilled)	15—20	1.5 vols. 70%
Mandarin Orange	70	2.5—4 vols. 70%; 1.5 vols. 80%
Neroli	2	2—2.5 vols. 70%
Nutmeg	8	1 vol. 80%; 4 vols. 70%
Orange	65	2—3 vols. 70%
Palmarosa	1.5	2 vols. 70%
Parsley	10	2 vols. 80%
Patchouli	4	1 vol. 95%
Pennyroyal	2	2 vols. 70%
Peppermint (American)	2	3 vols. 70%
Peppermint (Jap. dementholised)	2	2.5 vols. 70%; 6 vols. 60%
Peppermint (Mitcham)	2	2.5—3 vols. 70%
Petitgrain	2	1 vol. 80%; 3 vols. 70%
Pimento	1.5	1 vol. 70%
Pinus Sibirica (Abies)	2—3	3 vols. 70%
Rosemary (French)	2	2—3 vols. 75%
Rose Otto (Stearopteneless)	1.5—2	1—1.5 vols. 70%
Sage	6	2—2.5 vols. 75%
Sandalwood	1.5	3—5 vols. 70%
Sassafras	2	1 vol. 90%
Spearmint	4	2 vols. 75%
Spike Lavender	2	2 vols. 70%
Spike (Spanish)	1.5	2 vols. 70%
Thyme	2—3	2—3 vols. 70%
Vetivert	10	1 vol. 80%
Ylang (Manilla)	4—5	1—1.5 vols. 90%

ANTISEPTIC POWERS OF ESSENTIAL OILS

The antiseptic power of a number of essential oils was determined by W. H. Martindale, *Perfum. essent. Oil Rec.*, Nov., 1910. The *Lancet* carbolic acid coefficient using *B. Coli communis* was determined either in aqueous or in saponaceous solutions according to the solubility of the particular oil. As an outcome, saponaceous solutions of some essential oils are prepared under the name of perfumed Formosyls (*vide* Vol. I). The values found were as follows:—

Essential Oil	Carbolic acid co-efficient	Chief chemical constituents
Origanum Oil (A)	26	82% phenols, e.g., carvacrol.
Thymol (S)	25	
Carvacrol (S)	21	
Thymol (A)	19	
Thyme Oil (S)	15	46% phenols (thymol, etc.).
Thyme Oil (A)	13	46% phenols (thymol, etc.).
Geraniol (S)	12	
Cinnamon Leaf Oil (S) ..	10	86% phenols, e.g., eugenol.
Cinnamon Bark Oil (S) ..	9	52% aldehyde, e.g., cinnamic.
Clove Oil (S)	9	90% phenols, e.g., eugenol.
Cinnamic Aldehyde (S) ..	8	
Citronellol (S)	8	
Cinnamon Bark Oil (S) ..	8	82% aldehyde, e.g., cinnamic.
Cinnamon Bark Oil (A) ..	7	82% aldehyde, e.g., cinnamic.
Rosemary Oil (S)	6	
Otto of Rose (S)	6	68% alcohols estimated as geraniol.
Cassia Oil (S)	5	83.5% aldehyde, e.g., cinnamic.
Wintergreen Oil (S)	5	Methyl salicylate.
Eucalyptus Amygd. (S) ..	5	Phellandrene and eucalyptol.
Lavender Oil (English) (S) ..	5	Esters as linalyl acetate, 11%. Other constituents of the oil are linalool as such, esters other than the acetate, cineole and limonene.
Lemon Oil (S)	4	Limonene, citral, 4% to 7% citronellal, geranyl acetate, possibly other esters of geraniol and citronellal.
Almond Oil, Ess. s.A.P. (S)	4	Benzaldehyde chiefly.
Eucalyptol (S)	4	
Eucalyptus Glob. Oil (S) ..	4	67% eucalyptol together with pinene, phellandrene, alcohols and aldehydes.
Garlic Oil	2	Allyl sulphide chiefly.
Light Oil of Tar (Rect.) (S)	2	Volatile bodies. Contains no phenols.
Santal Oil (S)	1½	93.8% alcohol calculated as santalol, C ₁₅ H ₂₄ O.
Birch Tar Oil (S)	1½	Stated to contain guaiacol, cresol and pyrocatechin.
Cade Oil (S)	1	

(A) = Aqueous solution. (S) = Saponaceous solution.

These values have been confirmed and others added to the list by later investigators. The following are some of the more important references:—

Carbolic acid coefficients are given against a mixed culture of *Micrococcus catarrhalis* for a number of compounded perfumes. Isopropyl alcohol solutions have slightly greater bactericidal powers than ethyl alcohol solutions.—Dyche-Teague, *Perfum. essent. Oil. Rec.*, 1924, 6, 40 and 181; see also Bryant, *ibid.*, 252.

Germicidal value of some Australian essential oils. Certain oils could be used in place of phenol or cresols as preservatives in antisera.—Penfold, *Perfum. essent. Oil. Rec.*, 1924, 127.

The vapours of some essential oils have disinfecting activity with selectivity towards acid-fast bacteria.—Otto Schöbl, *Philipp. J. Sci.*, 1924, 443, per *Perfum. essent. Oil Rec.*, 1924, 330.

Oils of high carboic acid coefficient are more likely to lower surface tension. Extensive tables of Rideal-Walker coefficients are given.—S. Rideal, E. K. Rideal and A. Sciver, *Perfum. essent. Oil Rec.*, 1928, 285.

Physiological aspects of essential oils in relation to constitution. A table is given of Rideal-Walker coefficients for a large number of constituents of essential oils.—Malcolm Dyson, *Perfum. essent. Oil Rec.*, 1930, 287.

Germicidal values of commercial eucalyptus oils. The cineole-containing oils have not the highest antiseptic value.—Penfold, *Bull. tech. Mus.*, Sydney, 1933, No. 2.

For further references see "A Bibliography of Osmics," *Perfum. essent. Oil Rec. Yearbook*, 1928.

NOTES ON INDIVIDUAL ESSENTIAL OILS

For notes on essential oils not included in the following group, see under the corresponding drug, e.g., notes on *Oleum Caryophylli* are included under *Caryophyllum*.

OLEUM ABIETIS

Oleum Abietis (B.P. '32). Contains 35% to 45% w/w of esters, calculated as bornyl acetate, $C_{12}H_{20}O_2$. Sp. gr., 0.905 to 0.925. $\alpha_D -32^\circ$ to -45° . n_{D20° , 1.466 to 1.476. Soluble in an equal volume of alcohol (90%). Assayed by the B.P. method for esters, by saponification of 2 g. of the neutralised oil with 40 ml. of N/2 alcoholic potash during one hour on a water-bath.

In addition to oil of Siberian fir, there are several **pine-needle oils** of commercial importance. Oil of *Pinus sylvestris* has very variable characters according to the locality in which it is produced. Oil of *Pinus pumilio* was official in the B.P. '98; it is mainly produced in the Tyrol and has the following characters:—Sp. gr., 0.863 to 0.875; α_D , 1.475 to 1.480; n_{D26° , -4° to -15° ; esters as bornyl acetate, 3% to 8%.

In addition to the pine-needle oils, there are obtained by steam distillation from the stumps after the trees have been felled and from the branches and waste materials, both on the continent and in America, oils known as "**steam distilled pine oils**." These oils are the fractions collected after the light terpenes, which latter is sold as "**steam distilled turpentine**" or "wood turpentine," as distinct from "gum turpentine" obtained by distillation of the oleo-resin. The different fractions sold as "steam distilled pine oil" vary greatly in odour according to their boiling points; they are of the *Pinus palustris* type and are extensively used as ingredients in disinfectants, sprays and liquid soaps, and as solvents.

Yields of pine-needle oils from various species of Abietineæ.—Willner, *Quart. J. Pharm.*, 1933, 253.

ABIETIC ACID derivatives and decomposition products.—*J. chem. Soc. Abstr.*, i/1920, 232.

OLEUM AURANTII

Oleum Aurantii (B.P.C. '34). Residue on evaporation 2% to 4% w/w; sp. gr., 0.848 to 0.852 (sweet orange) or 0.852 to 0.856 (bitter orange). α_D , $+95^\circ$ to $+99^\circ$ (sweet orange) or $+88^\circ$ to $+96^\circ$ (bitter orange). n_{D20° , 1.472 to 1.474 (sweet orange) or 1.472 to 1.475 (bitter orange). The first 10% of the distilled oil has an optical rotation the same or only slightly lower than the original oil. *Oleum Aurantii*, U.S.P. X, is derived from fresh peel of the sweet orange only; sp. gr., 0.842 to 0.846 at 25° ; α_D , $+94^\circ$ to $+99^\circ$ at 25° ; n_{D20° , 1.4723 to 1.4737. Residue on

evaporation not above 100° , not less than 2%. The first 10% of the distilled oil has an optical rotation the same or not more than 2° away from that of the original oil and a refractive index from 0.0008 to 0.0015 lower at 20° .

The difference between bitter and sweet orange oils is not greater than the variations of analytical characters, flavour and odour so that they cannot be distinguished. **Tangerine orange oil** differs greatly from orange oil in flavour and aroma; it contains methyl anthranilate and methyl methylantranilate, and yields a distinctive terpeneless oil.

The principal varieties of orange oil commercially are Sicilian, West Indian, Californian, and recently S. African. The last two show a low residue on evaporation.

South African orange oil. Yield of oil and physical data.—*Perfum. essent. Oil Rec.*, 1930, 111.

Composition of Californian orange and lemon oils. A very complete report with methods of analysis and tabulated results.—Poore, U.S. Dept. of Agriculture, Tech. Bull. No. 241, per *Perfum. essent. Oil Rec.*, 1932, 166.

Residue on evaporation and other data.—C. T. Bennett, *Perfum. essent. Oil Rec.*, 1932, 2.

Terpeneless Oil of Sweet Orange. Berte (*Yearb. Pharm.*, 1924, 102) gives yield of terpeneless oil as 1.5% and the following figures:—Sp. gr., 0.883 to 0.900; α_D , $+25^{\circ} 50'$ to $+42^{\circ} 20'$; aldehydes as citral, 25% to 43%; esters as linalyl acetate, 14.8%. The sp. gr. is sometimes higher, up to 0.915.

A note from Sicily says the process of manufacture is exactly similar to that for terpeneless lemon oil, q.v., except that a larger quantity of terpenes are distilled off—about 95%. No physical or chemical data are known for the finished product, as it is only very rarely distilled, and then it is not a great success. The odour of the terpeneless orange oil does not pay for the distillation in many cases.—The terpeneless orange oils on the market are usually “synthetic” products, i.e., a mixture of which the chief odoriferous constituent is methyl methylantranilate. The distillation in London and elsewhere is carried out more scientifically than in Southern Italy.

Orange Flower Water is sold in many grades, and is sometimes found adulterated with the water obtained in distilling petit-grain oil (“Eau de Brouts”), and even with synthetic neroli. The following modified Legal’s test is characteristic of the genuine product. To 10 ml. of the sample add 0.5 ml. of 10% sodium nitroprusside solution and 2.5 ml. of 5% caustic soda solution, and, after 15 seconds, 0.5 ml. of glacial acetic acid. An emerald green colour is produced, and this changes to violet-red on the immediate addition of 2 ml. of 10% zinc sulphate solution.—*Perfum. essent. Oil Rec.*, 1924, 290.

PETITGRAIN. This name is given to the young orange fruits which fall naturally after “setting.” Oil of petitgrain is distilled from them.

PETITGRAIN OIL. Adulteration with terpinyl acetate. Detection by taking saponification value at 1 and 2 hours.—*Perfum. essent. Oil Rec.*, 1912, 3, 240.

Paraguay produces oil of petitgrain.—*Perfum. essent. Oil Rec.*, 1913, 414.

OLEUM BERGAMOTTÆ

Oleum Bergamottæ (*B.P.C.* '34). Contains not less than 36% of esters, calculated as linalyl acetate, $C_{12}H_{20}O_2$. Sp. gr., 0.882 to 0.886; α_D , $+12^{\circ}$ to $+24^{\circ}$; $n_{D20^{\circ}}$, 1.464 to 1.467. Residue on evaporation, 4% to 5% w/w, and the residue has an acid value of 20 to 50, and saponification value of 160 to 200. Complies with tests for absence of certain artificial esters, terpinyl acetate, and glyceryl acetate. **Oleum Bergamottæ**, *N.F. V*, contains not less than 36% of ester, as linalyl acetate; sp. gr., 0.875 to 0.880 at 25° ; α_D at 25° , $+8^{\circ}$ to $+24^{\circ}$. Tests for fixed oils and for chlorinated compounds are included.

Determination of adulteration with terpinyl acetate.—Schimmel's Reports, 911, 116, per *Yearb. Pharm.*, 1912, 75. Advantage is taken of the fact that terpinyl acetate is much less readily saponified than linalyl acetate.

OLEUM CAJUPUTI

Oleum Cajuputi (*B.P.* '32). Contains 50% to 60% *w/w* of cineole, $C_{10}H_{18}O$. Sp. gr., 0.916 to 0.926. α_D , not greater than -4° . n_{D20° , 1.462 to 1.472. Soluble in 2 volumes of alcohol (80%). Assayed by determination of the freezing-point of a mixture of 3 g. of the oil and 2.1 g. of *o*-cresol, the freezing-point being between 27.4° and 35.1° . **Oleum Cajuputi**, *U.S.P. X*, should be soluble in 1 volume of 80% alcohol; sp. gr., 0.912 to 0.925 at 25° ; n_{D20° , 1.4660 to 1.4710.

This is now required to be rectified, a process which increases the proportion of cineole. The upper limit of 60% for cineole is too low and excludes many high quality oils. The limit should be raised to 65%.—C. T. Bennett, T. T. Cocking and W. H. Simmons, *Pharm. J.*, ii/1933, 581.

OLEUM CEDRI

Oleum Cedri (*B.P.C.* '34). Sp. gr., 0.941 to 0.950; α_D , -25° to -46° ; n_{D20° , 1.495 to 1.510.

EAST AFRICAN CEDARWOOD OIL, from *Juniperus procera*, has an odour similar to that of American cedarwood oil, but the optical rotation is higher.—*Bull. Imp. inst. Lond.*, 1931, 29, 430; per *Quart. J. Pharm.*, 1932, 101.

MICROSCOPICAL CEDARWOOD OIL for use with immersion objectives and condensers, is a specially prepared oil, more viscous than the ordinary, and with refractive index adjusted to a definite figure. The oil to be used as a clearing agent in microscopy is the ordinary variety.

OLEUM CHENOPODII

Oleum Chenopodii (*B.P.* '32). Contains not less than 65% *w/w* of ascaridole, $C_{10}H_{16}O_2$. Sp. gr., 0.960 to 0.980; α_D , -4° to -8° ; n_{D20° , 1.474 to 1.479. Assayed by titration of the iodine liberated when an acetic acid (90%) dilution of the oil is allowed to interact for 5 minutes with a potassium iodide solution, hydrochloric acid and glacial acetic acid at -3° ; a blank titration is conducted, diluting with water before titration (see T. T. Cocking and Hymas, *Quart. J. Pharm.*, 1930, 253). The *U.S.P. X* assays the oil by measurement of the oil undissolved in an acetic acid; the oily layer should measure not more than 35%, indicating an ascaridol content of not less than 65% *v/v*. Sp. gr., 0.955 to 0.980 at 25° . α_D , -4° to -10° ; n_{D20° , 1.4723 to 1.4770.

The *B.P.* limits for sp. gr. and optical rotation will exclude some genuine oils.—E. J. Parry, *Chem. & Drugg.*, ii/1932, 154.

There is no prospect of basing an exact assay method on an iodometric process. The method of Cocking and Hymas gives satisfactory results but uses a factor which is 126.4% of the theoretical one.—K. Bodendorf, *Apothekerztg, Berl.*, 1930, 1636, per *Quart. J. Pharm.*, 1931, 106.

A statistical study of the physical constants of 39 samples of the oil. Ascaridole is in direct relationship to the sp. gr. and in inverse relationship to the solubility in alcohol (70%).—J. C. Munch and W. F. Reindollar, *J. Amer. pharm. Ass.*, 1931, 564.

OLEUM CITRONELLÆ

Oleum Citronellæ (*B.P.C.* '34). Estimated by the *B.P.* method for alcohols, which consists of determination of the ester values of the acetylated oil and of the original oil and calculation from a formula, it contains not less than 57% (for the Ceylon oil) or not less than 85% (for the Java oil) by weight of total acetylisable constituents calculated as geraniol. Sp. gr., 0·897 to 0·912 (Ceylon) or 0·885 to 0·900 (Java); α_D , -6° to -14° (Ceylon) or -2° to -5° (Java); n_{D20° , 1·479 to 1·485 (Ceylon) or 1·468 to 1·473 (Java). Yields a clear or slightly opalescent solution with 10 parts of alcohol (80%) and no globules separate after 24 hours at a temperature not lower than $15\cdot55^\circ$.

Examination of Citronella Oil. A method is given for the estimation of geraniol in the presence of citronellal. The oil is oximated by the method of Dupont and Labaune, the N determined by the Kjeldahl method giving the citronellal; another portion of the oximated oil is acetylated and the geraniol content found. Oils from Java, Celebes and Sumatra were examined.—Reclaire and Spoelstra, *Perfum. essent. Oil Rec.*, 1927, 130.

Determination of citronellal by means of hydroxylamine hydrochloride used at a low temperature.—*Analyst*, 1932, 773.

Formylation method shown to be unreliable.—C. T. Bennett, *Perfum. essent. Oil Rec.*, 1921, 351.

Alcohol as an adulterant.—E. J. Parry, *Chem. & Drugg.*, ii/1923, 390.

Determination of aldehydes. For a method of avoiding the difficulty caused by the insolubility of the citronellal sulphonate, as occurs in the usual bisulphite method, see F. D. Dodge, *Amer. Perfum.*, 1929, 24, 11; per *Quart. J. Pharm.*, 1929, 328.

OLEUM EUCALYPTI

Oleum Eucalypti (*B.P.* '32). By the freezing-point method of the *B.P.* as used for eucalyptol, oil of eucalyptus contains not less than 70% *w/w* of cineole. Sp. gr., 0·910 to 0·930; α_D , -5° to $+5^\circ$; n_{D20° , 1·458 to 1·470. Soluble in 5 volumes of alcohol (70%, sp. gr. 0·8896 to 0·8901). The *U.S.P. X* requires the congealing point of Oleum Eucalypti to fall not below $-15\cdot4^\circ$, corresponding to not less than 70% of eucalyptol.

Commercial Eucalyptus Oils. There are about ten eucalyptus oils met with in commerce, of which about seven are common. Their composition is very variable.

Species	Principal Constituents
<i>E. polybractea</i>	Cineole (77% to 84%), pinene.
<i>E. dives</i> (type)	Piperitone (40% to 50%), phellandrene.
<i>E. phellandra</i> (<i>amygdalina</i>)	Cineole (20% to 35%), pinene, terpineol, phellandrene.
<i>E. Australiana</i>	Cineole (68% to 72%), pinene, terpineol.
<i>E. elaeophora</i>	Cineole (65% to 76%), pinene.
<i>E. sideroxylon</i>	
<i>E. leucocylon</i>	
<i>E. citriodora</i>	
<i>E. oneorifolia</i>	Citronellal (70% to 85%).
<i>E. dives</i> var. "C"	Cineole (69% to 73%), and terpenes.
<i>E. Macarthuri</i>	Cineole (60% to 75%), terpineol and terpenes.
	Geranyl acetate (60% to 72%), geraniol, eudesmol.
<i>E. radiata</i>	Phellandrene in abundance, and piperitol.
<i>E. Consideriana</i>	Cineole (50% to 70%), pinene, phellandrene.
<i>E. phlebophylla</i>	Pinene and eudesmol.

Short monographs on the above are included, giving source, physical constants and composition. The oil of *E. Australiana* is sold in two fractions as "first hour oil" and "second hour oil." The former, which is the first oil obtained in the distillation, contains 70% to 82% of cineole, the latter contains only 25% to 40%. The author states that the oil has "no superior in aroma flavour, etc., and is undoubtedly the finest eucalyptus oil for medicinal purposes." The oil of *E. phellandra* is also collected and sold as "first" and "second hour" oils. Methods for the determination of cineole by Kleber and von Rechenberg's process and by the ortho-cresol method, as given in the report of the Essential Oil Sub-Committee on Uniformity of Analytical Methods (*Analyst*, 1927, 276), were found to give close agreement. A qualitative and also a quantitative test for piperitone in *E. dives* oil is given, and also a quantitative test for citronellal in *E. citriodora* oil, and for the esters in *E. Macarthuri* oil.—A. R. Penfold, *Bull. tech. Mus.*, Sydney, No. 2.

A number of physiological forms of *E. dives* exists yielding oils of widely different kinds:—

Oil	Piperitone	Cineole	Phellandrene
<i>E. dives</i> (type)	46% to 53%	absent	present
var. "A"	about 5%	"	"
var. "B"	10% to 20%	25% to 45%	"
var. "C"	less than 5%	60% to 75%	absent

—*J. roy. Soc., N.S.W.*, 1929, 61, 54.

A very complete description of the eucalypts, in which over 170 species are examined, is given in "A Research on the Eucalypts especially in regard to their Essential Oils," by R. T. Baker and H. G. Smith, *Bull. tech. Mus.*, Sydney, No. 24.

Eucalyptus oil distillation in the Nilgiris.—*Pharm. J.*, ii/1929, 54.

Eucalyptol (*B.P.* '32). $C_{10}H_{18}O = 154.1$. By determination of the f.p. of a mixture of 3 g. of the dried substance and 2.1 g. of *o*-cresol, a content of not less than 97.5% *w/w* of cineole, $C_{10}H_{18}O$, should be indicated. Sp. gr., 0.928 to 0.930; α_D , -1° to 1° ; n_{D20° , 1.456 to 1.460. F.p., not below 0° . Eucalyptol, *U.S.P. X*, should be optically inactive and comply with tests for phenols.

OLEUM GERANII

Oleum Geranii (*B.P.C.* '34). Contains not less than 21% of ester, calculated as geranyl tiglate, $C_{15}H_{24}O_2$. Sp. gr., 0.895 to 0.905 (French) or 0.894 to 0.904 (Algerian) or 0.888 to 0.896 (Bourbon); α_D , -7° to -11° (French), or -7° to -12° (Algerian) or -8° to -14° (Bourbon); n_{D20° , 1.465 to 1.470 (French) or 1.465 to 1.467 (Algerian) or 1.462 to 1.467 (Bourbon). Soluble in 3 volumes of alcohol (70%).

Geranium oil from S. Africa. Analytical characters given.—*Perfum. essent. Oil Rec.*, 1931, 102.

For the method of cultivation of geraniums for essential oil, see *Perfum. essent. Oil Rec.*, 1932, 173.

Experimental cultivation in Calabria. Yields of oil given.—*Perfum. essent. Oil Rec.*, 1934, 9.

OLEUM GRAMINIS CITRATI

Oleum Graminis Citrati (*B.P.C.* '34). Assayed by the *B.P.* method for aldehydes in Oleum Cinnamomi, by interaction of the neutralised oil in benzene solution with hydroxylamine reagent and titration with N/2 potash in alcohol (60%), it should contain not less than 75% *w/w* of citral, $C_{10}H_{16}O$. Sp. gr., 0.895 to 0.908;

α_D , -4° to $+1^\circ$. n_{D20° , 1.483 to 1.489. Soluble in 3 volumes of alcohol (70%), sometimes appearing opalescent in 10 volumes.

The oil is usually sold on its citral content and used for the preparation of citral. It should not be confused with **true verbena oil** which is obtained from *Lippia citriodora* (Fam. Verbenaceæ) and contains citral but is of much more delicate odour.

Spanish verbena oil is obtained from *Thymus hyemalis* (Fam. Labiatae).—*Perfum. essent. Oil Rec.*, 1912, 212.

OLEUM JUNIPERI

Oleum Juniperi (B.P.C. '34). Sp. gr., 0.870 to 0.890 (English) and 0.865 to 0.895 (Hungarian); α_D , $+1^\circ$ to -10° (English) and -5° to -15° (Hungarian); n_{D20° , 1.476 to 1.479 (English) and 1.479 to 1.484 (Hungarian). **Oleum Juniperi, U.S.P. X**, has a sp. gr. at 25° of 0.854 to 0.879; α_D at 25° , 0° to -15° and n_{D20° , 1.4790 to 1.4840.

Continental juniper berry oils are very variable in quality, probably due to their being by-products in the manufacture of other preparations. Italian oil is generally considered the best Continental oil.

English juniper berry oil is pre-eminently superior.—*Perfum. essent. Oil Rec.*, 1915, 63.

The effect of age on the oil is to increase its specific gravity and render it less soluble.—*Perfum. essent. Oil Rec.*, 1914, 5.

The Continental oil known as **juniper wood oil** is composed very largely of terpenes and has very little true juniper odour.

OLEUM LAVANDULÆ

Oleum Lavandulæ (B.P. '32). Is obtained from *Lavandula officinalis* Chaix and contains 7% to 14% w/w (English) or not less than 35% w/w (foreign) of esters calculated as linalyl acetate, $C_{12}H_{20}O_2$. Sp. gr., 0.882 to 0.900 (English) or 0.883 to 0.895 (foreign); α_D , -3° to -10° (English and foreign oils); n_{D20° , 1.459 to 1.470 (English) or 1.459 to 1.464 (foreign). Soluble with not more than a slight opalescence in 4 volumes of alcohol (70%). Determined by saponification of the esters by the B.P. method. The U.S.P. X requires Oleum Lavandulæ to contain not less than 30% of esters as linalyl acetate; sp. gr. at 25° , 0.875 to 0.888; α_D at 25° , -3° to -10° ; n_{D20° , 1.4600 to 1.4640. The volume of the oil should not diminish when shaken with water, a diminution indicating alcohol; a limit test for acetins is described by saponification of the 5% alcohol solution.

Continental lavender oil differs from English oil in having a much higher ester content. The proportion of esters in Continental oil, 25% to 60%, is very variable, depending on locality, cultivation, method of distillation and other factors. The esters in English oil vary from 7% to 14%, depending on season.

For discussion on the identity of the linalyl esters, see Dalton, *Perfum. essent. Oil Rec.*, 1926, 432; Langlais and Goby, *Perfum. essent. Oil Rec.*, 1926, 520; and Parry, *Perfum. essent. Oil Rec.*, 1927, 8.

English lavender oil comes intermediate between French and spike oils in cineole content.—Cocking, *Perfum. essent. Oil Rec.*, 1921, 339.

The figure obtained by the ortho-cresol method is not a true estimate of the cineole in oils that contain esters, and this method is not applicable to the estimation of cineole in French lavender oil.—Reed, *Perfum. essent. Oil. Rec.*, 1932, 340.

Oleum Lavandulæ Spicatæ (B.P.C. '34). Is obtained from *Lavandula stictifolia* Vill. and contains, when determined by the B.P. method for free alcohols, not less than 30% of free alcohols calculated as linalol. Sp. gr., 0.900 to 0.920; α_D , -4° to $+6^\circ$; n_{D20° , 1.462 to 1.469. Soluble in three volumes of alcohol (65%) and six volumes of alcohol (65%)

The quality of Spanish spike lavender oil is affected by the method of distillation. Steam distillation yields an oil of lower solubility but of superior odour to that obtained by open-fire distillation. According to Bordas (*Perfum. essent. Oil. Rec.*, 1927, 129) the open-fire method of distillation is almost universally employed in Spain, because the apparatus for steam distillation cannot be taken to the hills where the process is carried out. It is stated that though the physical data are important the odour of the oil is the criterion of quality, and that the range for the sp. gr. is 0.898 to 0.910.

Sage (*Perfum. essent. Oil Rec.*, 1927, 45) gives as a guide for Spanish spike oil the following figures:—Sp. gr. at 15.5° , 0.900 to 0.915; α_D at 25° , -5° to -10° ; n_{D20° , 1.464 to 1.466; solubility in 70% alcohol, 1 in 1.5 to 1 in 2.5; esters as linalyl acetate, 3% to 7%; total acetylisable, not less than 30%. See also Sage, *Perfum. essent. Oil Rec.*, 1923, 228, "An Analytical Symposium of the Spanish Essential Oils." French spike lavender oil differs very little from Spanish.

Lavandin Oil. In the districts of S. France where lavender and spike grow side by side, hybrids are formed from which lavandin oil is obtained on distillation. This oil is intermediate in odour value between true lavender and spike. It is generally sold on an ester content of 25%.

OLEUM LIMONIS

Oleum Limonis (B.P. '32). Contains not less than 4% w/w of aldehydes calculated as citral, $C_{10}H_{16}O$. Sp. gr., 0.857 to 0.861; α_D , $+57^\circ$ to 65° ; n_{D20° , 1.474 to 1.476. The U.S.P. X assays the oil by extraction during 30 minutes with phenylhydrazine solution (1 in 10) and titration with N/2 hydrochloric acid to methyl orange; it should contain not less than 4% of aldehydes as citral and have a sp. gr. at 25° of 0.851 to 0.855; α_D at 25° , $+57^\circ$ to $+64^\circ$, and n_{D20° , 1.4744 to 1.4755.

The Food and Drug Administration of the U.S. Dept. of Agriculture define oil of lemon for food purposes as the volatile oil expressed, without the aid of heat, from the fresh peel of the lemon with or without previous separation of pulp and peel. *Terpeneless oil of lemon*: oil of lemon from which all or nearly all the terpenes have been removed.—S.R.A., F.D. No. 2, Rev. 4, Aug., 1933.

Oil of lemon is obtained from fresh lemon peel by expression. This is accomplished either by pressing and absorbing the oil with a sponge by hand, or by the use of machines. It is anticipated that the machine process of extraction will supersede the sponge method (see *Chem. & Drugg.*, i/1929, 134, 234, 308, and *ibid.*, ii/1929, 289). It is stated that the machine-made oil is inferior in flavour to hand-pressed oil.

Method of preparation described. As a result of the standardisation of the oil to a content of 4% of citral, a large proportion of the oil exported from Sicily is doctored down with lemon terpenes to meet the minimum standard.—*Chem. & Drugg.*, ii/1927, 161.

The oil should not be exposed to light or air, and the presence of lemon juice also causes deterioration.—Finnemore.

An oil with an optical rotation exceeding $+76^\circ$ indicates that the oil has suffered deterioration; the acid value of the fresh oil is very low, increasing on keeping. Oil which has deteriorated gives a brown colour on shaking with hydrochloric acid.—*Chem. & Drugg.*, i/1928, 780.

Hydroxylamine process of estimating aldehydes and ketones including citral.—A. H. Bennett and F. K. Donovan, *Analyst*, 1922, 146; see also Report of the Essential Oil Sub-Committee on Uniformity of Analytical Methods, *Analyst* 1934, 105.

For the determination of the end-point with solution of hydroxylamine daylight or a daylight lamp is essential.—C. T. Bennett, *Pharm. J.*, i/1933, 150.

The *P.G. VI* requires the oil to be soluble clearly 1 in 12 in alcohol 90%, or to show only a little fluorescent matter, and to be free from fatty oils and paraffin.

Californian lemon oil, probably owing to the method of preparation, has a low residue on evaporation.

Oleum Limonis Deterpenatum (*B.P.C.* '34). Contains 40% to 50% *w/w* of citral. Sp. gr., 0.890 to 0.905; α_D , -4° to -9° ; n_{D20° , 1.479 to 1.483. Soluble in 3 volumes of alcohol (80%).

Terpeneless oil of lemon is mainly produced in S. Italy and Sicily. The lemon oil used is the finest obtainable. The yield is about 5% with the following characteristics:—

Sp. gr., 0.897 to 0.904; n_{D20° , 1.477 to 1.483; α_D , -2.0° to -3.5° ; citral content, 40% to 50%; solubility, 1 in 1 of 80% alcohol.

Citral obtained from lemon grass oil, if purified to such an extent that the verbena odour is removed, may be used as an adulterant as can be seen from the following figures:—

	Sp. gr.	α_D	Citral %
Sesquiterpeneless lemon oil	0.895	0 to -1	65
Terpeneless lemon oil ..	0.897 to 0.904	-2.0 to -3.5	40 to 50
Citral	0.896	0	100

The **ester content** is a guide to the detection of citral adulteration, but flavour and aroma are the best guides in conjunction with the analytical data.—Dalton, *Perfum. essent. Oil Rec.*, 1928, 7.

The removal of the sesquiterpenes from the oil causes it to lose its sweetness and softness, and the best oil for flavour and aroma is one containing under 40% of citral.—E. J. Parry, *Chem. & Drugg.*, ii/1913, 378.

OLEUM NEROLI

Oleum Neroli (*B.P.C.* '34). Soluble in 2 volumes of alcohol (80%) becoming turbid with more alcohol. Sp. gr. 0.870 to 0.885; α_D , 0° to $+8^\circ$; n_{D20° , 1.468 to 1.477. Saponification value, not more than 70. **Oleum Aurantii Florum**, *N.F. V* has a sp. gr. at 25° of 0.868 to 0.880; α_D at 25° , $+1^\circ 30'$ to $+5^\circ$. Complies with the same solubility test.

OLEUM PINI PUMILIONIS

Oleum Pini Pumilionis (*B.P.C.* '34). Contains not less than 4% *w/w* of esters, calculated as bornyl acetate, $C_{12}H_{20}O_2$. Sp. gr. 0.865 to 0.873; α_D , -6° to -15° ; n_{D20° , 1.470 to 1.480. The *U.S.P. X* oil is required to contain not less than 5% of esters as bornyl acetate; soluble in 10 volumes of alcohol (80%); sp. gr. at 25° , 0.853 to 0.869; α_D at 25° , $-4^\circ 30'$ to -9° ; n_{D20° , 1.475 to 1.4800. Less than 1% of the oil should distil below 165° .

OLEUM ROSÆ

Oleum Rosæ (*B.P.C.* '34). Should congeal at 18° to 22° and melt at 19° to 23° , when tested by the method of the *B.P.* for Oleum Anisi. Sp. gr. ($30^{\circ}/15.5^{\circ}$), 0.852 to 0.862; α_D , -2° to -4° ; $n_{D25^{\circ}}$, 1.458 to 1.465.

Bulgaria is now the principal otto-producing country.

Analytical Characters of Bulgarian Otto of Rose. Ethyl alcohol is stated to be a natural constituent of the oil; it should therefore not be washed before analysis. The stearoptenes content is very variable. The acid value varies from 1.4 to 3.8. A high refractive index and a high rhodinol content appear to be characteristic of good Bulgarian otto. Physical and analytical data given for a number of samples.—Garnier and Sabétay, *C. R. Acad. Sci., Paris*, 1933, 1748; see also *Perfum. essent. Oil Rec.*, 1934, 347. Any oil with less than 40% of rhodinol is suspect.

The presence of ethyl alcohol is doubtful and may be due to ethoxy, methoxy or other groups interfering with the Zeisel reaction. The ratio of citronellol to geraniol is a standard rather than the individual percentages of those constituents. Table of physical and analytical data with ratio $\frac{\text{geraniol}}{\text{citronellol}}$ is given. Parry and Seager, *Perfum. essent. Oil Rec.*, 1934, 213. See also *Perfum. essent. Oil Rec.*, 1933, 149, and Garnier, *Perfum. essent. Oil Rec.*, 1933, 370.

Details of cultivation and analysis of small samples of oil of rose in Cyprus.—*Perfum. essent. Oil Rec.*, 1930, 257.

GERANIOL $C_{10}H_{18}O = 154.144$ (three-quarters of the liquid portion), and citronellol $C_{10}H_{20}O = 156.16$ (the remaining 25%). Linalol is isomeric with geraniol, sp. gr., 0.870. B.p., 197° . It is contained in coriander, thyme and other oils and is either + or - rotatory.

Geraniol is an important base in perfumery. It is not made synthetically, but occurs in a number of oils, especially palmarosa and Java citronella—in these it is free, in other oils it occurs as ester: acetate and tiglate.

"RHODINOL" is a blend of the two alcohols geraniol and citronellol, from Pelargonium leaf oil. Some workers give the name as synonymous with geraniol—others as synonymous with citronellol.

75% or 76% at most is the highest amount of alcohol calculated as geraniol that should be allowed in a normal pure otto. Pure otto never has specific gravity as high as 0.862. Frequently it is as low as 0.850. Any otto with a refractive index below 1.4600 is adulterated, and almost invariably with alcohol. Considering that about 50% of the adulterated samples contain alcohol, which is used to adjust the high sp. gr. and refractive index of the geraniol compounds added, the following test is valuable:—

If 5 ml. be well shaken with 10 ml. of warm water and the mixture allowed to separate, the refractive index of the washed oil at 25° should not differ from that of the original oil by more than 0.0015 (absence of alcohol).

The determination of the refractive index should be made on the separated otto when quite clear, filtered if necessary, but not dried with any drying agent, since the original oil, owing to the method of distillation, is saturated with water.—Parry.

Although the predominating constituent, geraniol is by no means the most important, as both citronellol and nerol, and esters of the respective alcohols and other bodies, contribute largely to the fragrance of the oil. Phenyl ethyl alcohol, which possesses a mild odour, appears to be contained in otto and in neroli oil, not only as such, but also in the form of esters of benzoic and phenyl acetic acids. Although this alcohol is contained in exceedingly small quantity in otto, it represents quantitatively the chief volatile constituent of rose petals. Being freely soluble in water, it remains behind for the most part in the aqueous portion of the distillate from which the otto has been removed.

The so-called stearoptene of otto is a mixture of homologous hydrocarbons. The presence of otto in the air is readily recognised when only 0.000,000,000,000,333 g. of it is present in a cubic mm. of air.

OLEUM ROSMARINI

Oleum Rosmarini (*B.P.* '32). Contains not less than 2% *w/w* of esters as bornyl acetate, $C_{12}H_{20}O_2$, and not less than 9% *w/w* of free alcohols as borneol, $C_{10}H_{18}O$. Sp. gr., 0.900 to 0.919; α_D , -5° to $+10^\circ$; n_{D20° , 1.464 to 1.476. Soluble in 1 volume of alcohol (90%) and in 10 volumes of alcohol (80%). *Oleum Rosmarini, U.S.P. X*, contains not less than 2.5% of esters as bornyl acetate, and not less than 10% of total borneol, free and as esters. Sp. gr. at 25° , 0.894 to 0.912; α_D at 25° , 0° to $+15^\circ$; n_{D20° , 1.466 to 1.4720.

Spanish rosemary oil of really first quality can scarcely be distinguished from French oil, but the coarser quality is, as a rule, found on the market. For analytical characters see Maurice and Salamon, *Perfum. essent. Oil Rec.*, 1923, 231, also Simmons, *Perfum. essent. Oil Rec.*, 1923, 233.

The ester content of Spanish oil is usually below the *B.P.* limit.

For the characters of Sicilian essential oils, including rosemary, see Pellini, *Chem. & Drugg.*, ii/1923, 391, and for Yugoslavian oils see *Perfum. essent. Oil Rec.*, 1931, 62.

OLEUM RUSCI

Oleum Rusci (*B.P.C.* '34). Sp. gr., 0.920 to 0.955. Un-saponifiable matter, not less than 70%. A test for absence of fir tar is described. *Oleum Betulæ Empyreumaticum Rectificatum, N.F. V*, has a sp. gr. at 25° of 0.886 to 0.950 and complies with a test for distinction from oil of cade.

OLEUM SANTALI

Oleum Santali (*B.P.* '32). Contains not less than 2% *w/w* of esters, calculated as santalyl acetate, $C_{17}H_{26}O_2$, and not less than 90% *w/w* of free alcohols, calculated as santalol, $C_{15}H_{24}O$. Sp. gr., 0.973 to 0.985. α_D , -15° to -20° . n_{D20° , 1.500 to 1.510. Soluble at 20° in 5 volumes of alcohol (70%). The *U.S.P. X* oil has a sp. gr. at 25° of 0.965 to 0.980; α_D , -15° to -20° at 25° ; n_{D20° , 1.5040 to 1.5080.

Structure of the woods of sandalwood substitutes described.—*Perfum. essent. Oil Rec.*, 1931, 332. Kalamet, an Indian substitute.—*Perfum. essent. Oil Rec.*, 1932, 318.

Analytical characters of East Indian oil.—Clevenger, *Quart. J. Pharm.*, 1932, 590.

West Indian sandalwood oil is obtained from the wood of *Amyris balsamifera*. The oil is dextrorotatory. It contains amyrol, probably a mixture of alcohols which differ from santalol.

Oleum Santali Australiensis (*B.P.* '32). Contains not less than 90% *w/w* of free alcohols as $C_{15}H_{24}O$. Sp. gr., 0.970 to 0.976; α_D , -3° to -10° ; n_{D20° , 1.498 to 1.508. Soluble in 3 to 6 volumes of alcohol (70%).

Numerous papers have been published comparing East Indian and Australian sandalwood oils.

West Australian sandalwood oil of good quality is now available, containing 95% alcohol (calculated as santalol) and closely resembling the East Indian oil, although it has not been proved that the alcohols are identical with the santalols of the East Indian oil. The oil, which is obtained from *S. spicatum*

S. lanceolatum, is not inferior therapeutically to that obtained from *album*.—P. May, *Pharm. J.*, i/1928, 368.
 No evidence that the alcohols in W. Australian oil differ from those of Mysore and its therapeutic value is at least equal to that of *S. album*.—W. H. Monms, *Chem. & Drugg.*, i/1928, 171. See also a *contra* view.—A. R. Penfold, *m. & Drugg.* ii/1928, 496. *Earlier refs. in 18th Edn.*
 See also Venkatesaiya and Watson, *J. Soc. chem, Ind., Lond.*, Nov., 1928; Penfold, *Perfum. essent. Oil Rec.*, 1928, 417; and 1933, 46; also *ibid.*, 1932, 376.

For the volatile oil of Queensland sandalwood (*Santalum lanceolatum*), see Jones and Smith, *Perfum. essent. Oil Rec.*, 1931, 47.

For the therapeutic action of sandalwood oils, both Australian and East Indian, see Boldecker and Ludwig, *Pharm. Ztg., Berlin*, 1928, 73, 938, per *art. J. Pharm.*, 1928, 666. Australian oil has no antiphlogistic properties and its substitution for the oil of *Santalum album* is not permissible.

OLEUM SASSAFRAS

Oleum Sassafras (*B.P.C.* '34). Soluble in 3 volumes of alcohol (90%) the solution being neutral to litmus. Sp. gr., 0.70 to 1.084; n_{D20° , 1.523 to 1.531; α_D , $+1^\circ$ to $+5^\circ$. Oleum sassafras, *U.S.P. X*, should be soluble in 2 volumes of alcohol (90%). Sp. gr. at 25° , 1.065 to 1.077; α_D at 25° , $+3^\circ$ to $+4^\circ$; n_{D20° , 1.5250 to 1.5350.

Safrolum (*B.P.C.* '34). $C_{10}H_{10}O_2 = 162.1$. The m.p., determined by the *P.* method for Oleum Anisi, is not below 11° and the congealing point not below 10° . Sp. gr., 1.104 to 1.107; n_{D20° , 1.536 to 1.539. Soluble in 3 volumes alcohol (90%) and in 10 volumes of alcohol (80%).

OLEUM TEREBINTHINÆ

Oleum Terebinthinæ (*B.P.* '32). Sp. gr., 0.860 to 0.870; n_{D20° , 1.467 to 1.477. Iodine value, using a larger quantity of iodine monochloride and allowing absorption to proceed for exactly one hour, not less than 340. Residue, by rapid evaporation from a flat dish on a water bath, not more than 0.5%. The *U.S.P. X* oil has a sp. gr. at 25° of 0.854 to 0.868. n_{D20° , 1.4680 to 1.4780.

The *B.P.* specifies "oil distilled from the oleo-resin"; the oil so obtained is commercially known as "gum turpentine" to distinguish it from "wood turpentine" which is the first fraction obtained on the steam distillation of the stumps and waste. The two varieties closely resemble one another. For distinction between gum and wood turpentines see Parry, *The Chemistry of Essential Oils and Artificial Perfumes*, Vol. I, p. 18.

The optical rotation of turpentine derived from different species of *Pinus* compared.—Herty, *Yearb. Pharm.*, 1908, 199.

Examination of turpentine and turpentine substitutes. Wood turpentine may be detected by shaking with an equal volume of saturated sulphurous acid solution. Wood turpentine assumes a yellow colour, Russian and Swedish turpentine become greenish-yellow, and American and French turpentines remain colourless.—J. H. Coste, *Analyst*, 1908, 219.

A rapid method for the determination of petroleum in turpentine is given by Frey, *Svensk farm. Tidskr.*, 1908, per *Quart. J. Pharm.*, 1908, 201.

Lævo-pinene or **terebentene** of Berthelot is obtained by fractionation of French oil of turpentine as a colourless mobile liquid of characteristic odour. Sp. gr., 0.8767 at 0° and 0.8619 at 17.9° .

Dextro-pinene or **Australene**, the principal constituent of American turpentine, has the same sp. gr. and boiling-point, etc., as the French. α_D stated to be $+2.15^\circ$.

Russian Turpentine Oil. Authentic samples contain 40% to 70% distilled between 155° and 160° , and consisting chiefly of pinene. The oils arriving in the London markets have these "middle runnings" removed.

For making disinfectants it may not be of importance to have a large amount of hydrocarbon of relatively low boiling-point. Useful details tabulated.—E. Parry, *Chem. & Drugg.*, ii/1912, 340, 655; *Yearb. Pharm.*, 1913, 93.

Indian Turpentine, from *P. longifolia*, constituents of.—J. L. Simonson, *J. chem. Soc.*, May 1929, 570.

OREGON AND COLORADO DOUGLAS FIR OILS from trees grown in Britain. Geraniol the chief odorous constituent of the first. The odour of the other appears due to the large proportion of pinene and bornyl acetate.—C. Bennett, *Perfum. essent. Oil Rec.*, 1920, 218.

Terebenum (B.P. '32). Sp. gr., 0.862 to 0.87; α_D , -2° to $+2^\circ$; $n_{D_{20}}$ 1.471 to 1.474. Distils between 160° and 190° leaving only a slight viscous residue, and not less than 80% distils between 165° and 185° . Residue by rapid evaporation from a flat dish on a water-bath, not more than 2% w/w. The U.S.P. X required Terebenum to boil between 160° and 172° ; sp. gr. at 25° 0.860 to 0.865; α_D at 25° , not exceeding $+0.3^\circ$.

OLEA EXPRESSA

Notes on the more important fixed oils.

(For details on the composition and properties of these oils see Vol. I.)

OLEUM AMYGDALÆ

Oleum Amygdalæ (B.P. '32). Sp. gr., 0.915 to 0.920; $n_{D_{20}}$ 1.4624 to 1.4650; acid value, not more than 4.0; saponification value, 188 to 196; iodine value, 95 to 100. After remaining at -10° for 3 hours, it remains clear and does not congeal until about -18° . Complies with the tests for absence of apricot-kernel and peach-kernel oils, cottonseed oil, sesame oil and arachis oil. Oleum Amygdalæ Expressum, U.S.P. X, has a sp. gr. of 0.910 to 0.915 at 25° ; it should remain clear at -10° and not congeal until nearly -20° ; saponification value, 191 to 200; iodine value, 93 to 100.

Detection of Persic Oil in Almond Oil. The following modification of the B.P. nitric acid test will detect the presence of 5% of apricot-kernel oil. For 5 drops of oil are shaken with 4 drops of chloroform, and two drops of fuming nitric acid are then added separately down the sides of the tube, with 10 second interval between each drop. Apricot-kernel oil gives an immediate blood-red colour changing to brownish-red; peach-kernel oil gives a red colour within one minute; almond oil, a light brown colour within two minutes. Fresh mixtures of almond oil with 5% of apricot oil give a brilliant red within 5 minutes; old mixtures require 15 minutes to develop the full colour. Peach-kernel oil is not a commercial article and is probably never used as an adulterant of almond oil.—Z. anal. Chem., 1933, 94, 184.

OLEUM ARACHIS

Oleum Arachis (B.P. '32). Sp. gr., 0.916 to 0.920. $n_{D_{20}}$ 1.4625 to 1.4645; acid value, not more than 4; saponification value, 188 to 196; iodine value, 85 to 99. Complies with tests for absence of cottonseed oil, sesame oil and other vegetable oils.

To test for arachis oil in other oils, boil 1 ml. for 5 minutes under reflux condenser with 5 ml. of 1.5 N alcoholic potash, add 1.5 ml. acetic acid and 50 ml. of 70% alcohol, warm until clear, cool slowly to 15.5°; at this temperature it should remain clear for 5 minutes. If a precipitate is formed, 5 g. of the oil are refluxed for 5 minutes with 25 ml. of 1.5 N alcoholic potash and then 7.5 ml. acetic acid and 100 ml. of 70% alcohol, containing 1% hydrochloric acid, added. Keep at 12° to 14° for one hour and filter, washing with the alcohol hydrochloric acid mixture, at 17° to 19°. Dissolve the precipitate in hot 90% alcohol and cool to 15° for 2 to 3 hours. Wash any crystals and dissolve in ether, evaporate and dry at 100°. The m.p., and the m.p. after recrystallisation, should be below 71°. If no crystals are formed dilute the alcohol with 70% and keep at 17° to 19° for one hour.

OLEUM CHAULMOOGRÆ

Oleum Chaulmoogræ (*B.P.C.* '34). M.p. about 25°. Sp. gr. about 0.95 at 25°; specific rotation at 20° on a 10% *w/v* solution in chloroform, +48° to +52°; acid value 22 to 30; saponification value, 196 to 213; iodine value, 98 to 104. M.p. of the mixed fatty acids, 44° to 45°. **Oleum Chaulmoogræ**, *U.S.P. X*, complies with test for free acid, has a saponification value of 196 to 213, and an iodine value of 98 to 104.

Oleum Hydnocarpi (*B.P.* '32). Sp. gr. (25°/25°), 0.950 to 0.960; m.p., 0° to 25°; specific rotation of a 10% *w/v* solution in chloroform, not less than +53°; n_{D40° , 1.472 to 1.476. Acid value not more than 25; saponification value, 198 to 204; iodine value, 97 to 103.

Oleum Hydnocarpi Æthylicum (*B.P.* '32). Sp. gr., 0.905 to 0.910; n_D , not less than +45°; n_{D20° , 1.458 to 1.462; acid value, not more than 1.0; saponification value, 190 to 196; iodine value, 88 to 94.

OLEUM GOSSYPHII SEMINIS

Oleum Gossypii Seminis (*B.P.* '32). Sp. gr., 0.920 to 0.925; n_{D40° , 1.4645 to 1.4655; acid value, not more than 0.5; saponification value, 190 to 198; iodine value, 103 to 115. Particles of fat separate below 12° and it congeals between 0° and -5°. Complies with tests for absence of alkali, sesame oil and arachis oil.

Cottonseed oil may be detected in other oils by mixing in a tube 2.5 ml. of the oil with 1.25 ml. of amyl alcohol and 1.25 ml. of 1% precipitated sulphur in carbon disulphide and placing in a boiling water-bath; no reddish colour should develop within 30 minutes (Halphen's test). **Oleum Gossypii Seminis**, *U.S.P. X*, has at 25° a sp. gr. of 0.915 to 0.921; saponification value, 190 to 198; iodine value 105 to 114.

Oleum Lini (*B.P.* '32). Sp. gr., 0.930 to 0.940; n_{D40° , 1.4725 to 1.4750; acid value, not more than 5.0; saponification value, 187 to 195; unsaponifiable matter, not more than 1.5%; iodine value, 170 to 200. The *U.S.P. X* oil has a sp. gr. of 0.925 to 0.935 at 25°; iodine value, not less than 170.

OLEUM MORRHUÆ

Oleum Morrhuæ (*B.P.* '32). Sp. gr., 0·922 to 0·929; n_{D40} 1·4705 to 1·4745; acid value, not greater than 1·2; saponification value, 180 to 190; unsaponifiable matter, not more than 1·5% iodine value, 155 to 173. Remains bright when kept at 0° for 3 hours. 0·04 g. in chloroform gives a blue colour not paler than that of a standard blue glass on the addition of 2 ml. of antimony trichloride reagent. *Oleum Morrhuæ, U.S.P. X*, has a sp. gr. of 0·918 to 0·927 at 25° and an iodine value of 140 to 180. Minimum limits for vitamins A and D are also specified (*vide infra*).

THE VITAMINS OF COD-LIVER OIL

Cod-liver oil contains vitamins A and D in varying amounts. The Revision Committee of the U.S.P. has announced the new Pharmacopœial standard for Cod-Liver Oil, which became official on Jan. 1, 1935, as (a) the minimum vitamin A standard for U.S.P. cod-liver oil shall be not less than 600 International vitamin A units per gramme, and (b) the minimum vitamin D standard for U.S.P. cod-liver oil shall be not less than 80 International vitamin D units per gramme. This minimum would have caused the rejection of 35 out of 200 samples of cod-liver oil examined by the Pharmaceutical Society of Great Britain in the last few years. Actually the Society rejected 17 samples whose vitamin D potency was less than 60 International units per gramme. The minimum potency of 85 units adopted by the U.S.P. has lately been accepted also by the Pharmaceutical Society. Most samples of cod-liver oil have a vitamin D potency between 100 and 250 International units per gramme; occasionally samples are found to have 300 or 350 units per gramme. The vitamin A potency ranges from about 1000 to 3500 International units per gramme, though occasionally samples are found to have a lower or a higher value than these.

There is no correlation between the vitamin A and the vitamin D values of a sample of cod-liver oil. The following table of values found recently for 23 samples of cod-liver oil in the Pharmaceutical Society's Laboratories shows this:—

Vitamin A and D Value of Twenty-three Samples of Cod-Liver Oil Examined Biologically

Sample	Vitamin A International Units	Vitamin D International Units
1	1,500	160
2	1,500	360
3	500	80
4	650	85
5	1,500	210
6	3,600	250
7	2,000	120
8	8,400	150
9	4,500	80
10	1,500	80
11	3,000	300
12	3,700	300
13	1,500	330
14	4,800	300
15	1,500	340
16	2,250	240
17	1,250	220
18	2,750	60
19	1,500	290
20	2,000	50
21	1,500	110
22	2,850	250
23	750	180

The vitamin value of cod-liver oil seems to vary inversely with the yield of oil from any particular liver or batch of livers. The origin of the vitamins in cod-liver oil is almost certainly the diet of the cod, namely herring, whiting, codlings in the North Sea, and squid and caplin round the Newfoundland banks. Since, however, these have only a low vitamin content, it must be concluded that the cod itself uses little of the vitamin obtained from its food but stores it in the liver for some unknown reason.—Drummond and Hilditch, Empire Marketing Board Publication, No. 35, 1930, H.M.S.O.

One U.S.P. X vitamin A unit, one "Sherman unit," and one vitamin A unit of the American Drug Manufacturers Association are each approximately equivalent to 1.4 I.U.

One I.U. of vitamin D is approximately equivalent to 3.25 vitamin D units of the American Drug Manufacturers Association.

One Steenbock unit of vitamin D is approximately equivalent to 2.7 I.U. One I.U. of vitamin D is approximately equivalent to 1.66 Oslo units.—Per *Chem. & Drugg.*, i/1934, 704.

Blue values determined by the B.P. method on 67 oils purchased from retail chemists were obtained ranging from 3.5 to 20.0 and the average was 7.8. The average blue value obtained on 36 samples via the unsaponifiable matter was 27.0. The best values for average oil are:—direct blue value = 9.3; blue value via unsaponifiable matter = 21.8. The best values obtained by spectrophotometric examination are:—extinction coefficient (1% solution in 1 cm. cell) at 328 m μ = 0.587 (on oil) and 0.505 (via unsaponifiable matter); percentage of vitamin A = 0.0315. The biological assays of bulked samples gave the following results:—vitamin A = 670 units per gramme; vitamin D = 81 units per gramme.—R. S. Morgan and H. Pritchard, *Analyst*, 1935.

An Alternative Colorimetric Method. The determination of vitamin A in cod-liver oil can be made by a colour test in which the oil is heated with a chloroform solution of catechol and antimony trichloride. The violet-red colour obtained is compared as soon as it is formed with a 0.01% solution of potassium permanganate. The colour is said to be more stable than the blue colour obtained with antimony trichloride alone.—E. Rosenthal and J. Erdélyi, *Biochem. J.*, 1934, 28, 41.

Effect of Light on Vitamin A Potency. Exposure of cod-liver oil to any source of white light of sufficient intensity results in "delumination"—disappearance of normal golden fluorescence—and destruction of vitamin A. Kept for some months in the dark it regains much of its fluorescence but vitamin A is permanently destroyed.—P. R. Peacock, *Lancet*, ii/1926, 329.

Cod-liver oil emulsions can be kept for at least 4 months without appreciable loss of vitamin A potency, and probably for 7 or 8 months without serious alteration, if stored in well-stoppered, amber glass bottles and kept in the dark.—H. N. Griffiths, T. P. Hilditch and J. Rae, *Analyst*, 1933, 65.

Variations in Oils from Different Sources. The 5th Report of the Imperial Economic Committee on Marketing and preparing for Market of Foodstuffs Produced within the Empire states that for relative richness in vitamins Scottish oils rank first, then Newfoundland, then Norwegian, but the last is usually the best from the marketable aspect of colour and odour. Newfoundland oils do not find a ready sale in Gt. Britain—the price is often high. In Gt. Britain the market value of cod-liver oil depends less on its true medicinal value than on its acceptability by the public.—*Chem. & Drugg.*, ii/1927, 357.

NORWEGIAN COD-LIVER OIL INDUSTRY. Bergen is the centre of the industry. Yield of oil in 1928 (a poor year) was 50,000 hectolitres, against 70,000 in 1927. In marketing, some of the dealers fill the air space above the oil with CO₂ and nitrogen to prevent oxidation.

Unsaturated Fatty Acids in the Oil. Cod-liver oil is composed almost entirely of unsaturated fats. An increase in the amount of unsaturated fatty acids in the environment of the tubercle bacillus tends to disintegrate it. An increase of unsaturated fatty foods yields an increase of the same in the blood, and the bacillus is present in the blood in comparatively early cases of phthisis. Increase of saturated fat above a certain point retards its absorption from the intestine. The saturated fat is assimilated up to about 14% only; unsaturated, on the other hand to the extent of 98%. In a mixed diet the unsaturated help the saturated to become absorbed. The highly unsaturated acids contained serve the immediate needs of energy production and the saturated are stored in the nature of a reserve.

Cod-liver oil should be prepared under conditions preventing oxidation, both from the aspect of this theory and the vitamin content.

Cod-liver oil is a food—it enters into permanent combination with a body cell yielding energy to it and altering the whole of the cell's relations by becoming an integral part of the cell protoplasm. It is more readily absorbed than other fats and has probably a marked action on metabolism.

The greater part of the fat obtained from animal tissues is not real fat, but complex combinations of fatty acids with glycerophosphoric acid and nitrogen-containing compounds—the so-called phosphatides—this is the portion actually made use of by living cells. Phthisical patients treated with cod-liver oil have been observed and effects on *nitrogen metabolism* found to be marked and the beneficial effect on *fat absorption* to be considerable.

The total activity of cod-liver oil does not reside in its vitamin D, or in A + D, any more than quinine represents the total activity of cinchona bark. Attention is drawn to the phosphatides and the high content of *unsaturated fatty acids*.—J. W. England, *J. Amer. pharm. Ass.*, 1929, 116.

Oleum Hippoglossi. Halibut-liver oil is described in the *B.P.C.* '34, but no standard is specified. The natural variations, particularly in vitamin content, are very great.

Blue values and iodine values of samples of halibut-liver oils of known origin compared with those of samples of the commercial oil and mixtures with cod-liver oil.—R. T. M. Haines and J. C. Drummond, *J. Soc. chem. Ind.*, Lond., 1934, 81T.

The "blue values" of samples of halibut-liver oil examined varied from 300 to 1720.—R. T. M. Haines and J. C. Drummond, *Brit. med. J.*, i/1933, 558.

Vitamin A Content of Fish-liver Oils (other than Cod). The range of vitamin A concentration is at least 2500 : 1 and is not parallel with vitamin D potency. The liver oils of haddock, whiting, skate of medium or small size, codling, and immature or small fish generally, are poor in vitamin A. Oils from pollack, saithe, hake and ling are similar in potency to cod-liver oil; salmon, turbot, sturgeon and especially halibut yield liver oils rich in vitamin A. The larger halibut occurring in northern waters yield the better liver oil. Unlike the oils of other fish, halibut-liver oil shows a seasonal variation in vitamin A content independent of the spawning period. The oil is richest in vitamin A in May, subsequently falling, and rising to a second smaller maximum in September. There is possibly a connection between vitamin A content and the abundance of planktonic organisms from which the fish probably obtain carotene for conversion to the vitamin.—J. A. Lovern, J. R. Edisbury and R. A. Morton, *Biochem. J.*, 1933, 1461.

It is the practice to standardise oils for sale to a definite vitamin A content. This may be done either by mixing strong and weak halibut-liver oils to give the desired vitamin content or by diluting a strong halibut-liver oil with another fish-liver oil, such as cod-liver oil, or even with a vegetable oil. There seems no objection to this practice, but if any other oil is added the product cannot be described as natural halibut-liver oil. The following variations were found in 33 samples of halibut-liver oils obtained during two seasons: Blue value, 205 to

7,100; vitamin A $E_{1\%}^{1\text{cm.}}$ 328 $\text{m}\mu$, 6.8 to 144; sp. gr., 0.922 to 0.9286; n_{D40° , 1.470 to 1.488; iodine value, 111 to 171; saponification value, 150 to 175; unsaponifiable matter, 8.3% to 21.5%.—N. Evers and W. Smith, *Pharm. J.*, i/1935, 417.

Sodii Morrhuas (*B.P.C.* '34). Forms a clear solution in 10 parts of warm water.

Comparison of five samples showed that "Sodium Morrhuate 10%" is very differently interpreted by different makers and that some standards should be laid down and conformed to. Iodine value varied from 148 to 226.5, colour from clear yellow to turbid orange, and fatty acid content from 7.0% to 9.45%.—R. T. M. Haines, *Lancet*, i/1933, 748.

Liquor Ergosterolis Irradiati (*B.P.* '32). Contains in 1 g. approximately 3000 units of antirachitic vitamin D. The unit of vitamin D is the activity contained in a specified quantity of solution issued by the National Institute for Medical Research, London, and adopted as the International standard.

Liquor Vitaminæ A (B.P.C. '34). Contains in 1 g. approximately 60,000 units. The unit is the activity of 0.0006 mg. of a sample of β -carotene kept in the National Institute for Medical Research, London, and adopted as the International standard.

OLEUM OLIVÆ

Oleum Olivæ (B.P. '32). Sp. gr., 0.915 to 0.918; n_{D40° , 1.4605 to 1.4635; acid value, not more than 2.0; saponification value, 190 to 195; iodine value, 79 to 88. Complies with tests for absence of sesame oil, cottonseed oil and arachis oil. The U.S.P. X oil has a sp. gr. of 0.910 to 0.915 at 25° and an iodine value of 79 to 90.

Test For Tea-Seed Oil. (Bieber's Reagent.) Prepare a mixture of concentrated nitric acid, concentrated sulphuric acid and water, equal parts by weight. Of this mixture 10 ml. is well shaken in a test-tube with 10 ml. of the oil to be analysed, and placed in boiling water for twenty minutes. Should tea-seed oil be present to the extent of 20% or more, the oil layer changes to a cherry-red colour. The colour varies with the amount and quality of tea-seed oil present, the crude oil gives a deeper colour. When cool, samples of pure olive oil solidify to a yellow, nearly white, mass, while the adulterated oil remains liquid or semi-solid, according to the amount of tea-seed oil present, having the characteristic colour.—J. Cofman Nicoresti, *Pharm. J.*, i/1920, 129.

It is impossible either by chemical or physical constants or by available colour tests to ascertain whether olive oil is adulterated with tea-seed oil.—H. A. Caulkin, *Yearb. Pharm.*, 1927, 616.

The production of olive oil has made great strides in California and South Australia. The colour of the oil varies considerably from water-white to golden-yellow. Low-class oils have a green tinge. It should taste pleasant and soft, but the taste varies according to the locality, etc. Thus oils from Tuscan olives are more palatable than those from Ligurian olives. An oil may be quite pure and unadulterated but be inferior on this point. The large quantity of edible oils produced in Tunis is frequently admixed with the best brands of French and Italian edible oils to cover the harsh flavour.

Excluding abnormal oils, a high iodine absorption may indicate adulteration with as little as 5% of a drying oil or 15% of sesame, cottonseed, and rape oils. The saponification value will only lead to definite results if large quantities of rape oil have been added. In the elaidin test, olive oil yields of all oils the hardest elaidin, and also solidifies most quickly, but this test can only be used as a preliminary. The examination of unsaponifiable matter is necessary if the addition of lard is suspected. Green olive oils should be tested for copper.—*Chem. & Drugg.*, i/1928, 461, q.v. for further data.

The elaidin test does not assist in the differentiation of olive and tea-seed oils and the chief difference between the two is shown by the iodine values of the unsaponifiable matter.

In the present state of knowledge it is not possible to give standards for olive oil or cod-liver oil which will prevent adulteration. Quite large proportions of tea-seed oil can be added to olive oil, and of other fish liver oils to cod-liver oil, without bringing their analytical characters outside the limits for normal oils. The tests for arachis, cottonseed, and sesame oils will not ensure their complete absence. In these cases it is necessary to rely on the statement that the oil "is the oil obtained from"—N. Evers, *Pharm. J.*, i/1933, 195.

Oleum Persicæ (B.P.C. '34). Sp. gr., 0.917 to 0.921; n_{D40° , 1.464 to 1.465; acid value, not more than 8; saponification value, 189 to 193; iodine value, 100 to 110.

Oleum Rapæ (B.P.C. '34). Sp. gr., 0.913 to 0.917; n_{D40° , 1.463 to 1.467; acid value, not more than 5; saponification value, 171 to 177; iodine value, 97 to 105; unsaponifiable matter, 0.6% to 1.2%.

OLEUM RICINI

Oleum Ricini (*B.P.* '32). Sp. gr., 0·958 to 0·969; n_{D40° , 1·4695 to 1·4730; acid value, not more than 4·0; saponification value, 177 to 187; iodine value, 82 to 90; α_D , not less than +3·5. Remains bright when kept at 0° for 3 hours. **Oleum Ricini**, *U.S.P. X*, has a sp. gr. of 0·945 to 0·965 at 25°; saponification value, 179 to 185; iodine value, 83 to 88.

OLEUM SESAMI

Oleum Sesami (*B.P.* '32). Sp. gr., 0·921 to 0·924; n_{D40° , 1·4650 to 1·4665; acid value, not more than 4·0; saponification value, 188 to 193; iodine value, 103 to 112. Complies with tests for absence of cottonseed oil and of arachis oil. The test for absence of sesame oil in other oils consists of agitating 2 ml. of the oil with 1 ml. of a 1% *w/v* solution of sucrose in hydrochloric acid and standing for 5 minutes, when the acid layer should not appear pink.

Oleum Sojæ (*B.P.C.* '34). Sp. gr., 0·924 to 0·927; n_{D40° , 1·4675 to 1·4685; acid value, not more than 5; saponification value, 190 to 194; iodine value, 130 to 137; unsaponifiable matter, 0·7% to 1·5%.

OPIUM

Opium (*B.P.* '32). Contains in its moist state as imported not less than 9·5% of morphine calculated as anhydrous. Assayed by the *B.P.* method: 8 g. mixed thoroughly in a mortar with 30 ml. of water and 2·0 g. of calcium hydroxide is transferred to a tared flask, with water to 90 g.; after shaking for 30 minutes, the mixture is filtered and 52 ml. of the filtrate (equivalent to 5 g. of the opium) shaken with 5 ml. of alcohol and 25 ml. of ether. 2·0 g. of ammonium chloride added, shaken for 5 minutes and occasionally during 30 minutes, the total time of shaking being 15 minutes, and stood overnight; the ethereal layer is decanted on to a plug of cotton wool in a funnel, the flask and contents and filter rinsed with 10 ml. of ether, and the filter with a further 5 ml. in small portions; the aqueous liquid is then poured through the filter, and the flask and filter washed with morphinated water till free from chloride; the crystals on the filter are washed back into the flask, boiled with excess N/10 sulphuric acid, and the cooled liquid titrated with N/10 sodium hydroxide to cochineal or methyl red, a correction of 0·052 being added.

Opium, *U.S.P. X*, is assayed by a similar process, on the water soluble matter, and should yield not less than 9·5% of anhydrous morphine. Opium, *P.G. VI*, when dried at 60°, contains not less than 12% of anhydrous morphine.

International Assay Process. A report of a Commission of Experts for the Standardisation of Methods for Determining the Morphine Content of Raw Opium described an assay process which was published, with some comment

y Prof. L. van Itallie, in the *Bulletin de la Fédération Internationale Pharmaceutique*, 1933, 14, 98. The following is a translation:—

The samples are mixed in such a way as to give a homogeneous mass, or, if the original opium is dry, a homogeneous powder. For analysis, the whole of this powder is passed through a sieve of which the maximum width of mesh is 0.30 mm.

The determination is carried out in three parts. (1) Determination of the loss of weight on drying at 103° to 105° (moisture). (2) Determination of the amount of extractive soluble in water in the presence of calcium hydroxide under the conditions of the process. (3) Determination of the morphine content.

Determination of the Loss in Weight on Drying (Moisture). Weigh 1 g. of opium (to within ± 5 mg.) in a weighing-bottle with a ground-in stopper; heat for two hours at 103° to 105° and weigh. Continue heating until the loss in weight after 1 hour in the oven is not more than 0.005 g. The loss in weight is calculated on 100 g. of the opium being analysed and in the following formula this percentage loss is denoted by the letter F . When dealing with soft opium the mass is diluted with a little water and dried in a thin layer.

Determination of the Extractive and of the Morphine. Triturate in a mortar 4 g. opium (weighed to within ± 5 mg.) with 1 g. of calcium hydroxide and 10 ml. of water so as to produce a homogeneous mixture. Dilute with another 10 ml. of water and set aside the mixture for 15 minutes, stirring frequently. Then by means of small quantities of water transfer the mixture to a small tared flask and add water until the contents of the flask weigh 45 g. (weighed to within 1 g.). Cork the bottle and shake vigorously and continuously for 30 minutes. Pour out the contents of the bottle on to a glass filtering funnel No. 3G3 of Schott and Gen, Jena, or on to a filtering funnel of similar pattern but having the same porosity and suitable dimensions. The liquid is at first allowed to flow freely, then the slightest possible suction is applied. Part of the filtrate is used to determine the extractive and part for the determination of the morphine.

A. DETERMINATION OF THE CONTENT OF EXTRACTIVE. Concentrate on a water-bath 3 g. of the filtrate (weighed to within ± 0.1 g.), then dry the remainder at 103° to 105° until the loss in weight after drying for one hour is not greater than 0.003 g. The weight of the remainder, in mg., is used for determining the extractive (E) given by 100 g. opium, according to the following formula:—

$$E = \frac{(100 + F) M}{3 - M}, \text{ where } M \text{ denotes the weight in grammes of the residue}$$

from 3 g. of the filtrate and F the percentage of moisture in the opium.

B. DETERMINATION OF THE MORPHINE CONTENT. In a 50 ml. Erlenmeyer flask, or in some other suitable vessel, weigh 25 g. of filtrate (to within ± 0.1 g.) and add 2.5 ml. of alcohol (90%) and 12.5 ml. of ether. Close the flask, shake it to mix the liquids and add 1 g. of ammonium chloride. Shake well for 5 minutes, then frequently during 30 minutes. Set aside the mixture in the closed flask until the next day. Shake well to detach the precipitated morphine and pour the contents of the flask as completely as possible on to a filtering funnel No. 3G4 of Schott and Gen, Jena, or on to a filtering-funnel of similar pattern, but having the same porosity and suitable dimensions. Avoid wetting the upper part of the funnel. Filter the liquid completely with the help of slight suction, then wash the flask with 3 ml. of ether; pour the latter on to the filtering funnel and without using suction wash it by inclining and shaking, then filter the ether completely by suction. The washing of the flask and the filtering funnel is repeated in the same way, each time with 3 ml. of water saturated with morphine, until the filtrate gives no reaction for chlorides. Heat the flask, in which there may still remain a little morphine, and the glass filtering funnel containing the greater part of the morphine, for 30 minutes at a temperature of 103° to 105°. After cooling, grease the upper and inner part of the filtering funnel to a depth of 0.5 cm. with soft paraffin; then fix it by means of a cork into a 300 cm. filtering flask. Warm 10 ml. of methyl alcohol in the flask (preferably with a reflux condenser because of the toxicity of the vapour of methyl alcohol) to dissolve the remaining crystals of morphine attached to it; pour the warm solution on to the filtering funnel without applying suction, dissolve the greater part of the morphine by shaking, and filter the solution using suction. This operation is repeated twice, using each time 10 ml. of methyl alcohol. Then, by means of a small wash-bottle rinse all the deposits of morphine which may have formed on the filtering funnel and on the lower tube with 10 ml. of methyl alcohol; pour this alcohol into the filtering flask. The impurities in the morphine will thus remain on the plate of the filter. Verify whether the filtrate is quite

clear; should a little morphine be precipitated dissolve it by warming slightly. Add to the clear liquid 5 to 10 drops of methyl red and titrate with N/10 hydrochloric acid or N/10 sulphuric acid to a faint orange. Dilute the liquid with 120 ml. of freshly boiled and cooled water, which changes the colour of the solution to yellow; and complete the titration by adding N/10 acid until the liquid begins to turn red.

The morphine content is calculated according to the following formula:

$$(a) \text{ in } \% \text{ of anhydrous opium } \frac{(1000 + E + F) (A + 1) 0.114}{100 - F}$$

$$(b) \text{ in } \% \text{ of original opium } \frac{(1000 + E + F) (A + 1) 0.114}{100}$$

E = percentage yield of extractive in the presence of calcium hydroxide calculated on the opium.

F = percentage of moisture in the opium.

A = ml. of N/10 acid used in the titration.

This formula allows for a correction of 1 ml. of N/10 acid (equivalent to 0.0285 mg.) for the morphine remaining in solution.

Some Defects in the International Process. The process is undoubtedly superior to many published methods, and particularly to the official methods of most foreign pharmacopœias. It is, however, much more complicated and troublesome to perform than the method of the British Pharmacopœia and it is extremely doubtful whether it is superior or even equal to the latter method as regards accuracy.

Its principal disadvantages are:

- (1) The very small weight of opium used for the test.
- (2) The unnecessarily involved practical details, some of which could quite well have been dispensed with without appreciably diminishing the accuracy of the results.
- (3) The decidedly clumsy manipulation, such as the weighing of all liquids, the method adopted for the initial filtration and the directions for the collection, washing and solution of the morphine. Some of these defects cannot fail to cause very appreciable errors.

If the process is performed exactly as described, it appears very improbable that close agreement between different analysts using the method will occur. In order to produce a really accurate method capable of giving reasonably consistent results in different hands very considerable modifications would be needed, some of which might very well be in the direction of simplification.

Varieties. Turkey opium is produced in Asiatic Turkey and occurs in rounded, conical, irregular or flattened masses usually enveloped in poppy leaves, and sometimes more or less covered with the winged fruits of a species of *Rumex*. The weight of the cakes varies from about 1 oz. to several pounds, the majority of the pieces varying from about 1 lb. to 4 lb. Turkey opium includes the varieties "Soft Shipping" opium and "Druggists" opium. European opium is produced chiefly in Bulgaria, Greece and Yugoslavia; it resembles the "Soft Shipping" variety of Turkey opium in its general characters. Persian opium occurs in brick-shaped masses weighing about 1 lb., or rarely in cones or sticks of varying weight. The bricks are usually wrapped in red paper and tied with red or yellow string, but occasionally white paper is employed. It usually contains varying proportions of certain native gums added during manufacture to obtain a product suitable for moulding. Indian medicinal opium, which is used for medicinal purposes in India, occurs in square blocks weighing about 2 lb. and wrapped in paper which is sometimes oiled. It varies considerably in consistence, the moisture content ranging from 10% to 18%. Indian smoking opium occurs in balls, about the size of a small Dutch cheese, which are enveloped in a casing made from poppy petals. Russian opium has the characters of soft Persian opium and is usually wrapped in paper.

Constituents. Opium contains morphine in proportions varying from 5% to 21% of the dried opium. The morphine exists in combination with meconic and sulphuric acids in the form of salts readily soluble in water. The "Soft Shipping" variety of Turkey opium contains about 15% to 18% of morphine while "Druggists" opium of good quality contains about 12% to 16%. Dried European opium contains from about 15% to 21% or occasionally more. Persian opium contains about 10% to 12% and occasionally as much as 13.5%. Undried Indian medicinal opium has varied considerably at different times, sometime containing as little as 7%, and sometimes as much as 12%. Narcotine range

from 1.5% to 12.5%. Codeine exists to the extent of 0.3% to 4%, Indian opium containing the highest proportion and Turkey opium the lowest. The remaining alkaloids constitute about 1 % of the drug. They include thebaine, narceine, papaverine, meconidine, codamine, laudanine, laudanosine, neopine, lanthopine, protopine, cryptopine, rhœadine, oxynarcotine, pseudo-morphine, gnoscopine, xanthaline (papaveraldine), tritopine, hydrocotarnine, porphyroxine (in Indian opium) and possibly others. Meconin, meconoidin and opionin are indifferent substances, present in small proportions only. Other constituents are mucilage, sugar, wax and rubber, together with salts of calcium, magnesium and potassium.

Determination of morphine, narceine, narcotine, papaverine, codeine and thebaine in opium.—B. Kljotschkina, *Arch. Pharm., Berl.*, 1933, 271, 558, per *Quart. J. Pharm.*, 1934, 119.

Manufacture of Morphine from Opium. Raw opium made into a thin paste with water is poured into boiling milk of lime and after a few minutes boiling the mixture is filtered from the precipitated calcium meconate. The mixed filtrate and washings are concentrated and treated with ammonium chloride, the ammonia being removed by boiling. The greyish sludge of morphine is dissolved in hydrochloric acid, the solution decolourised, evaporated to dryness and the morphine hydrochloride purified by recrystallisation.—*Pharm. J.*, i/1934, 635.

Extraction of Opium Alkaloids. The plant is extracted with warm water and an equal volume of alcohol and excess ammonia is added, precipitating morphine and narcotine, the latter being separated by treatment with benzene or chloroform, in which morphine is insoluble. The mother-liquors are treated with dilute acetic acid, and from this papaverine can be extracted with benzene. The strong bases, codeine and thebaine, forming salts, remain in solution, and can be separated by the addition of alkali which precipitates thebaine, codeine remaining in solution.—*J. chem. Soc. Abstr.*, i/1925, 153.

Addiction to Opium, Morphine, Cocaine, etc. See individual chapters Vol. I.

Opium Pulveratum (B.P. '32). Adjusted with lactose to contain from 9.5% to 10.5% of morphine, calculated as anhydrous. Opium Pulveratum, U.S.P. X, yields from 10% to 10.5% of anhydrous morphine.

Tinctura Opii (B.P. '32). Contains 0.95% to 1.05% *w/v* of morphine, calculated as anhydrous. Assayed by evaporation of 80 ml., trituration with 5 ml. of water, addition of 20 ml. of water and 2 g. calcium hydroxide, followed by addition of water to 86 g., then proceeding as for opium, taking 52 ml. of the filtrate equivalent to 50 ml. of the tincture. Alcohol content, 41% to 46% *v/v*. Tinctura Opii, U.S.P. X, contains 0.95% to 1.05% *w/v* of anhydrous morphine, and has an alcohol content of 17% to 19% *v/v*.

Tinctura Opii Camphorata (B.P. '32). Contains 0.045% to 0.055% *w/v* of morphine, calculated as anhydrous. Assayed by extraction of the residue, after evaporation, with calcium hydroxide solution, cleaning the solution with ether, addition of ammonium sulphate and extraction with twice the volume of chloroform-alcohol mixture (1 : 1) followed by extraction with chloroform-alcohol mixture (1 : $\frac{1}{2}$); after evaporation of the solvent, the residue is dissolved in N/1 hydrochloric acid and diluted with water to N/10 solution. The brownish colour produced by a 20 ml. portion of the solution on addition of 8 ml. of 1% sodium nitrite solution and 12 ml. of dilute ammonia solution is matched against a standard solution of morphine in N/10 hydrochloric acid. Alcohol content, 56% to 60% *v/v*. Tinctura Opii Camphorata, U.S.P. X, is not standardised; it contains approximately 0.04% *w/v* of morphine; alcohol content, 43% to 46%.

Æthylmorphinæ Hydrochloridum (B.P.C. '34). $C_{19}H_{23}O_3N, HCl, 2H_2O = 385.7$. Loss at 100°, not more than 10%. Ash, not more than 0.1%. A morphine limit equivalent to 0.1% of anhydrous morphine is included by matching against a standard solution, the colour produced by 5 ml. of a 2% solution in N/10 hydrochloric acid on the addition of 2 ml. of 1% sodium nitrite solution and 3 ml. of dilute ammonia. Æthylmorphinæ Hydrochloridum, U.S.P. X, loses not more than 10% at 100°.

Æthylmorphine Sulphate, $(C_{17}H_{18}O_2NOC_2H_5)_2, H_2SO_4, 5H_2O$, is soluble 1 in $9\frac{1}{2}$ of water at 15.5° and 1 in 111 of alcohol 90%.—J. L. Thomson, *Pharm. J.*, i/1920, 7.

Apomorphinæ Hydrochloridum (B.P. '32). $C_{17}H_{17}O_2N, HCl, \frac{1}{2}H_2O = 312.6$. Loss at 100°, not more than 5%. Ash, not more than 0.1%. 0.1 g. shaken with

5 ml. of ether should produce not more than a faint red colour (due to decomposition products). The *U.S.P. X* salt complies with the test for decomposition products and is rejected if it produces immediately an emerald-green colour when shaken with 100 parts of water.

Codeina (*B.P. '32*). $C_{18}H_{21}O_3N, H_2O = 317.2$ M.p. of the dried substance 155° to 156° . Loss at 100° , not more than 6%. Ash, not more than 0.1%. 5 ml. of the 2% *w/v* solution in N/10 hydrochloric acid, with 2 ml. of 1% sodium nitrite solution and 3 ml. of dilute ammonia solution, produces a yellow colour not deeper than 5 ml. of 0.002% *w/v* solution of anhydrous morphine in N/10 hydrochloric acid, similarly treated. Codeina, *U.S.P. X*, loses not more than 6% at 80° ; a test for morphine with ferric chloride and potassium ferri-cyanide is included.

Codeinæ Phosphas (*B.P. '32*). $C_{18}H_{21}O_3N, H_3PO_4, H_2O = 415.2$. Loss at 100° , 4% to 7%. Complies with the limit test for morphine. The *U.S.P. X* salt contains not less than 67% of anhydrous codeine, by extraction from solution with sodium hydroxide by chloroform and titration with N/10 sulphuric acid to methyl red.

Diamorphinæ Hydrochloridum (*B.P. '32*). $C_{21}H_{23}O_5N, HCl, H_2O = 423.7$ Ash, not more than 0.1%. A morphine limit, as indicated by the colour produced in N/10 hydrochloric acid solution with sodium nitrite and ammonia, is included and is equivalent to 1.5%.

Morphina (*B.P.C. '34*). $C_{17}H_{19}O_3N, H_2O = 303.2$. Loss at 110° , not more than 7%. Ash, not more than 0.1%. Complies with the limit test for other alkaloids in Morphinæ Hydrochloridum, using three-quarters the quantity of substance.

Quantitative methods for the determination of Morphine, Codeine and Diamorphine in tablets are described in Methods of Analysis (*A.O.A.C.*, 1930, 461).

Solubility in carbon tetrachloride is 0.0156 g. in 100 g. at 18° to 22° .

Spectrum lines characteristic for morphine are obtainable with 1/200 grain.—J. J. Dobbie, *Lancet*, i/1913, 1399.

Bromophenol blue recommended as indicator for titration of morphine. A 1% solution of morphine hydrochloride has a pH of 3.65.—N. Evers, *Yearb. Pharm.*, 1921, 325.

Morphine and other alkaloids in animal excreta. Detection in organs, urine, etc.—*Yearb. Pharm.*, 1922, 12.

The fate of morphine in the animal body, with a method of estimation in body fluids and tissues.—*J. Pharmacol.*, June, 1927, 177.

All the acyl compounds of morphine, e.g., diacetylmorphine and benzoylmorphine, are readily decomposed and morphine recovered from them, whereas the alkyl derivatives, such as codeine and benzylmorphine, are intimate compounds from which the morphine cannot be recovered. The former are strong narcotics like morphine, and the latter only weak narcotics.—D. B. Dott, *Pharm. J.*, ii/1928, 250.

Morphinæ Acetas (*B.P.C. '34*). $C_{17}H_{19}O_3N, C_2H_4O_2, 3H_2O = 399.2$. Ash not more than 0.1%. Complies with the limit test for other alkaloids.

Morphinæ Hydrochloridum (*B.P. '32*). $C_{17}H_{19}O_3N, HCl, 3H_2O = 375.7$. Loss at 120° , not more than 12.5% and the dried material is not more than faintly yellow in colour. Ash, not more than 0.1%. Limit of other alkaloids extracted with chloroform from sodium hydroxide solution, not more than 1.5% Morphinæ Hydrochloridum, *U.S.P. X*, should lose not more than 15% at 100° . A test for apomorphine is described.

GREGORY'S SALT.—An impure morphine hydrochloride, being a mixture of double salt of morphine hydrochloride and codeine hydrochloride occurring in the manufacture of morphine.

Morphinæ Sulphas (*B.P.C. '34*). $(C_{17}H_{19}O_3N)_2, H_2SO_4, 5H_2O = 758.5$. Loss at 130° , not more than 12%. Ash, not more than 0.1%. Complies with the limit test for other alkaloids. The *U.S.P. X* also allows a moisture loss of 12% at 130° , and tests for acidity, ammonium salts, meconate and foreign alkaloids are included.

Morphinæ Tartras (*B.P. '32*). $(C_{17}H_{19}O_3N)_2, C_4H_6O_6, 3H_2O = 774.4$. Loss at 100° , not more than 7%. Ash, not more than 0.1%. Complies with the limit test for other alkaloids.

Papaveretum (*B.P.C. '34*). Contains from 47.5% to 52.5% of anhydrous morphine. Assayed by the *B.P.C.* process: extract 1 g. in 20 ml. of water and

ml. of N/1 sodium hydroxide with successive portions of 50 ml. and 25 ml. of ether; transfer the aqueous liquid (filtering if necessary) to a 50 ml. flask, and washings of the ether layers with 2.5 ml. of N/1 sodium hydroxide with 50 ml. of water, and 5 ml. portions of water until 50 ml. has been collected; then transfer to a conical flask, add 5 ml. of alcohol and proceed as the *B.P.* for Opium, collecting the morphine on a small filter paper, and adding a correction of 0.025 g. of morphine to the amount indicated by the titration. *Opium concentratum, P.G. VI*, is a mixture of the hydrochlorides of opium alkaloids containing 48% to 50% of morphine.

Papaverina (*B.P.C.* '34). $C_{20}H_{21}O_4N=339.2$. M.p., 146° to 147° . Ash, not more than 0.1%. Papaverinum hydrochloridum is official in the *P.G. VI*.

Thebaine Hydrochloride. Thebainum hydrochloridum is official in the *Helv. V*, and contains when dried not less than 99% of $C_{19}H_{21}O_3N, HCl$; should contain from 2% to 3% of water corresponding to approximately half a molecule of water.

OXYGENIUM

Oxygenium (*B.P.* '32). $O=16.000$. Contains not less than 98% *v/v* of O_2 , the residue consisting of argon with a trace of nitrogen, and a trace of hydrogen. Assayed by absorption in one-fifth its volume of alkaline solution of pyrogallol. The turbidity produced in barium hydroxide solution should not exceed that produced by sodium bicarbonate solution equivalent to a limit of CO_2 of approximately 0.0002% *w/v*. Limit tests for halogens, acids or alkalis, and oxidising substances are included. Oxygenium, *U.S.P. X*, contains not less than 98% *v/v* of O . The limit of carbon dioxide is one quarter of that of the *B.P.*

Oxygen Content of the Air. 212 determinations during period of 10 months, April 1911 to January 1912, showed no material fluctuation despite all possible variations in climatic conditions, including periods before, during and after the vegetative season. The averages were 20.952% oxygen and 0.031% carbon dioxide which maintain the results of Cavendish in 1783 and de Marli in 1787 as to the uniformity of air as regards its oxygen content.

The interdependence between the amounts of oxygen and carbon dioxide is so constant that estimations of the latter made in the Loudin apparatus may be taken as accurate indications of the oxygen content, e.g., for every 0.01% increase in carbon dioxide a corresponding increase in the percentage of oxygen may be assumed.—*Nature, Lond.*, i/1913, 409.

Air Liquefying Apparatus (Hampson's Patent). This apparatus depends upon a method by which a moderate amount of refrigeration, produced by the expansion of a gas, may be accumulated and intensified till it reaches the point at which the gas becomes liquid under atmospheric pressure. The method consists in directing all the expanded gas immediately after its expansion, over the coils which contain the compressed gas that is on its way to the expansion point. The cold developed by expansion in the first expanded gas is thus communicated to the on-coming compressed gas, which consequently expands from, and therefore to, a lower temperature than the preceding portion. It communicates in the same way its own intensified cold to the succeeding portion of compressed gas, which in its turn is made colder both before and after expansion than any that had gone before. This intensification of cooling goes on until the expansion temperature is far lower than it was at starting, and the effect is so powerful that even the small amount of cooling due to the free expansion of gas through a throttle-valve may be made to liquefy air without using other refrigerants.

The amount of refrigeration due to free expansion was ascertained by Joule and Thomson, and is in the first place proportional to the fall of pressure. Air at 0° is cooled 0.29° for every atmosphere of pressure-drop. This cooling, however, increases with the descent of the temperature from which expansion takes place, and the law is that it is inversely proportional to the square of the absolute temperature. Thus expansion of air from $4\frac{1}{2}$ atmospheres to 1, and from a temperature of 0° , i.e., 273° Absolute, gives about 1° of cooling in the

air itself. But when the air expands from $\frac{2}{3}$ of that absolute temperature, i.e. from 91° absolute, the cooling for the same pressure drop is $\frac{9}{4}$ of 1° , or $2\frac{1}{4}^{\circ}$.

In the liquid state air occupies $\frac{1}{800}$ th part of its ordinary volume, or in other words, if liquid air be vaporised and restored to normal temperature it will expand 800 times.

Vacuum Vessels (Thermo-Isolators). Are necessary for the storage of liquid air and those gases which only liquefy at low temperatures.

They are either cylindrical or globular, and consist of one glass vessel enclosed within another. The space between these vessels is thoroughly exhausted and sealed under a high permanent vacuum. Heat radiates across the vacuum space very slowly, consequently liquid stored in a vacuum vessel is admirably insulated from the action of external heat and only vaporises slowly.

The efficiency of the vacuum vessel is increased by silvering since radiation from outside is thus partially reflected.

Liquid air evaporates from vacuum vessels at the rate of from 5% to 15% per 24 hours, according to the size of the vessel, the evaporation from small vessels being more rapid than from large.

Hydrogen Liquefying Apparatus (Morris W. Travers'). It has been found that hydrogen, when compressed at normal temperatures and allowed to expand in an apparatus like the Hampson Air Liquefier, does not become cooled but on the contrary slightly heated. When, however, its temperature is reduced to -80° , or lower, before it enters the regenerator coil, it becomes further cooled on free expansion, so that the principle of self-intensive cooling employed in Hampson's Air Liquefier can then be applied to the liquefaction of this gas.

HYDROGENIT is said to be a mixture of dry soda-lime and ferro-silicon or other silicon alloy. When acted upon by heat, 3 kilos give about 1 cubic metre of hydrogen.—per *Pharm. J.*, i/1912, 31.

CALCIUM HYDRIDE or **HYDROLETE**, CaH_2 , is used as hydrogen generator by decomposing with water.

Ferrosilicon process. Ferrosilicon falls into sodium hydroxide solution (covered with hydrocarbon oil to prevent frothing). Also other processes. Silicon alloy is also used.—*Pharm. J.*, ii/1915, 214.

Nitrogenii Monoxidum (*B.P.* '32). Nitrous oxide drawn from a cylinder in the upright position, contains not less than 93% *v/v* of N_2O . Carbon monoxide limit, determined on the first portion of the gas drawn from the upright cylinder, 50 parts per million *v/v*. Complies with tests for absence of halides and sulphuretted hydrogen, arseniuretted hydrogen and phosphoretted hydrogen, and with limit tests for water vapour, carbon dioxide, uncondensable gases, acidity or alkalinity, reducing substances and oxidising substances. Nitrogenii Monoxidum, *U.S.P. X*, complies with tests for carbon dioxide, halogens, acids or alkalis, and reducing substances.

PANCREATINUM

Pancreatinum (*B.P.* '32). Possesses not less than a minimum activity in respect to trypsin, lipase and amylase. To determine trypsin activity due to trypsin, 50 ml. portions of skimmed milk, standardised to protein content, are adjusted to pH 8.0 with $\text{N}/10$ sodium hydroxide using phenol red as external indicator; one portion is boiled and 10 ml. of a 0.5% boiled solution of the substance added and to the second portion 10 ml. of a 0.5% solution is added, both are heated rapidly and maintained at 37° to 40° for $1\frac{1}{2}$ hours, cooled rapidly and neutralised with $\text{N}/10$ sodium hydroxide to phenolphthalein. Add to each 5 ml. of a neutralised solution of formaldehyde and titrate with $\text{N}/10$ sodium hydroxide to phenolphthalein; the boiled mixture requires 4.9 to 5.1 ml. and the other 9.0 to 13 ml. Activity due to lipase determined by digestion of two 10 ml. portions of a suspension

parated cream in N/10 sodium carbonate containing 0.2% *v/v* oleic acid and adjusted with acetic acid to pH 8.0, one with 1 ml. of a 1% solution of the pancreatin and the other with 1 ml. of the same solution previously boiled, at 38° to 40°, for 4 hours; after dilution with an equal volume of alcohol, the titration with N/20 sodium hydroxide to phenolphthalein should not be less than 10 ml. Amylase is determined by adding to 5 ml. portions of a 1% starch mucilage containing 0.5% salt, 0.35, 0.40, 0.45, 0.50, 0.55 and 0.60 ml. of a 0.02% solution of the pancreatin and maintaining at 40° for one hour; after cooling rapidly to 20° and adding one drop of N/10 iodine to each, the portions with addition of 5 ml. or more should show no blue colour.

Pancreatin, *U.S.P. X*, converts not less than 25 times its weight of starch into soluble carbohydrates and not less than 25 times its weight of casein into proteoses.

The effect of certain chemicals and drugs on the action of pancreatin was examined by Martindale (see also Edn. XVII, p. 126) by means of the following test:—One quarter of the average doses of the substances were mixed with 150 ml. of a 3.5% casein solution prepared by aid of 0.35% sodium carbonate. 2 ml. of an active pancreatin solution was then added. This gave the equivalent of an average dose of the "drug" in 570 ml. (1 pint) of liquid, this is bearing some relation to the conditions *in vivo*.

Notable incompatibles were acids in general, alcohol, calcium chloride, ferric chloride, manganese sulphate, manganese hypophosphite, quinine hydrochloride and dihydrochloride, and syrup of ferrous iodide.

The information is important in regard to the prescribing of pancreatic extracts with other preparations and with regard to effects *in vivo* when the above medicines are given.

Experiments to determine the effect of chemicals on the amylolytic action of pancreatin are described in Edn. XIX, Vol. II, p. 142: it was found that the sample of pancreatin in question was well up to standard when tested for amylolytic power; and a liquid preparation of commerce, which had strong proteolytic power, was found to be practically useless for amylolysis. Cf. Malt diastase results.

Papainum (*B.P.C.* '34). Assayed by the *B.P.C.* '34 process: 0.2 g. in a few ml. of water is washed into 30 ml. of a neutral 4% casein solution, 10 ml. of N/10 sodium carbonate added and diluted to 50 ml.; a 20 ml. portion with 10 ml. of water and 20 ml. of neutral formaldehyde solution is titrated with N/10 hydrochloric acid to phenolphthalein; the remaining 30 ml. of the solution is maintained at 37° for 6 hours and a 20 ml. portion titrated as before; calculated from the difference between the titrations, the amino acids produced by 1 g. of papain require for neutralisation not less than 20 ml. of N/10 sodium carbonate. Ash limit, 1%.

Pepsinum (*B.P.* '32). Dissolves not less than 2500 times its weight of coagulated egg albumen. Assayed by digestion, at 40° to 41° for 6 hours, of a solution of pepsin and salt in water acidified with hydrochloric acid with a titration of freshly prepared egg albumen in acidified water, when no granules should be visible and the liquid not more than faintly opalescent. Pepsinum, *U.S.P. X*, should digest not less than 3000 times its weight of freshly coagulated and disintegrated egg albumen. The digestion is conducted at 52° during 2½ hours, and the volume of undigested albumen measured.

FR. CX. requires that the pepsin shall convert 25 times its weight of dried fibrin. Digest pepsin 0.1, dilute hydrochloric acid 1.5, water 58.5, fibrin 2.5 for 6 hours at 50°; test the filtrate with nitric acid. Pepsin amylocée and pepsin crocée in dose 0.25 g. are to contain sufficient pepsin to carry out the above test.

Pepsinum, *P. Helv. V*, is standardised against a known weight of casein and diluted if necessary with lactose; the moisture should not exceed 5% and the ash 3.5%.

Assay. A tentative quantitative method for the determination of pepsin in liquids is described in Methods of Analysis (*A.O.A.C.*, 1930, 464).

The *B.P.* assay process, retained from the *B.P.* '14, is unsatisfactory, and should never be used except as an empirical limit test, since it does not measure the amount of egg albumen dissolved. Pepsin is only manufactured in two strengths, and dilution of the lower strength should not have been sanctioned. *Pharm. J.*, ii/1932, 146.

After consideration of a number of methods proposed for the assay of pepsin, that described by Cole (*Practical Physiological Chemistry*, 9th Edn., p. 228) based on the clotting of calcified milk, is recommended.—A. C. Munro and R. Seif. *Pharm. J.*, i/1933, 482.

As the result of the examination of 13 different samples of pepsin, it was concluded that commercial pepsins on the English market to-day are of good quality. A discussion and comparison of the *B.P.*, *U.S.P.*, *P.G.*, and *Edinburgh* methods of assay is given, and figures are deduced showing the comparative severity of the tests. Suggestions are made for an improved official assay process. The greatest obstacles in the way of obtaining comparable results in the test for pepsins is shown to be the variability of the substrate. In the case of egg-white, two methods of overcoming this difficulty are:—(a) the setting-up of a standard pepsin with which other pepsins are to be compared in tests using the same egg-white for tests and standard, or preferably (b) the use of a method of averaging the results of several tests.—K. Bullock, *Quart. J. Pharm.*, 1935, 10.

CARMINE FIBRIN, prepared by washing blood fibrin with ammoniacal solution of carmine, is a dark coloured mass, easily crumbled, which yields no colour to water or 0.1% hydrochloric acid until the fibrin contained in it has been dissolved by a ferment; hence its use as a simple quantitative test for pepsin, noting the time required to give a pink colour equal to that of a standard or control.

The effect of certain chemicals and drugs on the action of pepsin was investigated by W. H. Martindale to show approximately the relative inhibitory action *in vitro* which certain chemicals and drugs have on the digestive power of pepsin. The conditions under which the experiments were conducted were:

3 g. of egg albumen, prepared as for testing pepsin (*B.P.*), were placed in 30 ml. of hydrochloric acid, 0.2%. An average dose (in most cases) of the drug was added, followed by 1 ml. of freshly prepared pepsin solution containing 0.2% of pepsin (*B.P.*). These mixtures were then incubated at 38° for 2 hours, this length of time being allowed to permit of the pepsin utilising its power to the utmost. It is to be noted that 30 ml. of fluid is a small amount in comparison with the capacity of the human stomach, but the results are comparable, and it is evident that if the drugs in question do not interfere with peptic activity in this strong concentration, they are certainly not likely to do so when more diluted. On the other hand, if peptic activity is interfered with, there is evidence of physiological incompatibility.

The following apparently **do not interfere** with peptic activity to any extent:—

LIST A.

Acidum Acetylsalicylicum	Elixir Aromaticum	Magnesii Sulphas (small dose)
„ Benzoicum	„ Papaini	Migralgine
„ Boricum	Ext. Cascaræ Liq.	Naphthaleni HCl
„ Cacodylicum	„ Cinchonæ Liq.	Pancreatinum
„ Hydrochloricum	„ Cocæ Liq.	Phenacetinum
„ Hypophos. Dil.	„ Ergotæ Liq.	Phenol
„ Phosphoricum	„ Hydrast. Liq.	Phosphorus
„ Salicylicum	„ Ipecac. Liq.	Physostigmini Sulphas
Æther	„ Nucis Vom. Liq.	Picrotoxinum
Alcohol (small amount)	Guaiacolis Camphoras	Pilocarpinæ Nitras
Amidopyrina	„ Carbonas	Podophylli Resina
Caffeinæ Citras	Hydrarg. Perchlor.	Sodii Aminarsonas
Calcii Glycerophosph.	„ et Pot. Iod.	„ Cacodylas
Chloroformum	Hydrogenii Peroxidum	Syrupus Ferri Iodidi
Cocainæ Hydrochlor.	Hyoscine HBr	Theobromina
Codeinæ Hydrochlor.	Liq. Arsen. Hydrochl.	Thiosinamina
Diamorphinæ	„ Chloromorphiæ	
Hydrochloridum	„ Hamamelidis	
	„ Morphinæ	
	Hydrochloridum	

For further information regarding these experiments see Edn. XIX, Vol. p. 145.

Pepsin Solution. Loss of activity on storage. A mixture containing pepsin in acidified chloroform water showed a reduction of 40% in activity after a fortnight. A concentrated solution, containing 4 g. per fluid ounce of chloroform water but no acid, was stable.—A. C. Munro and R. Seifert, *Pharm. J.*, i/1933, 432.

Seriparium (*B.P.C.* '34). Rennet (rennin) should comply with the following test:—Mix 0.1 g. with 50 ml. of water, allow to stand for 15 minutes and add 1 ml. to 50 ml. of milk of acidity to phenolphthalein equivalent to 0.14% to 0.15% of lactic acid warmed, in a beaker about 12 cm. high and 5 cm. in diameter, to 43°; stir slowly for 10 seconds and maintain at 43°; thickening commences within 10 minutes, and a firm curd is produced within an additional 30 seconds, indicating coagulation of not less than 25,000 times its weight of fresh cows' milk. Renninum, *N.F. V*, complies with the same test.

Rennin differs considerably from pepsin. It is a decomposition product of protein, of acid albumin type, not precipitated by boiling the solution (*cf.* pepsin). It dialyses through parchment but is hydrolysed in the process (the main bulk in the case of pepsin is not dialysed). Rennin is precipitated on saturating the liquid with sodium chloride. Proteolytic activity does not seem to be a part of the true physiological characteristics of rennin.—*J. Amer. chem. Soc.*, 1923, 249, per *Chem. & Drugg.*, i/1923, 437.

Muller's Trypsin Test. A method of testing the activity of trypsin preparations consists in placing small quantities of the trypsin preparations to be tested from a platinum loop, upon a Löffler blood serum plate and incubating 12 hours at 55° to 60°. In good products a depression should be made on the serum with a dilution 1 : 1000.—*Practitioner*, Jan., 1913. See also Sorensen's Test, *Pharm. J.*, ii/1912, 137, and *Brit. med. J.*, i/1912, 584.

Lysozyme. A ferment-like substance which has the power of killing and dissolving bacteria and which is found in most of the secretions—the tears and nasal mucus having the highest content—and all the tissues of man, and is present in the tissues of other animals and some vegetables. It has an extraordinary bacteriolytic effect on non-pathogenic bacteria. It is suggested that lysozyme is one of the primal protections of the cell against bacterial invasion. The onset of keratomalacia in animals fed on a diet deficient in vitamin A can be prevented by the instillation of human tears into the animal's eyes, whereas normal salt solution has no protective action. The direct bactericidal action of the tissues and secretions is an important factor in natural immunity.—A. Fleming, *Lancet*, i/1929, 217.

PARAFFINUM

Paraffinum Durum (*B.P.* '32). M.p., 50° to 60°. Ash, not more than 0.05%. Paraffinum, *U.S.P. X*, melts between 50° and 57°.

Paraffinum Liquidum (*B.P.* '32). Sp. gr., 0.880 to 0.895. 50 ml. at 37.8° flows from a Redwood viscometer in not less than 260 seconds. Petrolatum Liquidum, *U.S.P. X*, has a kinematic viscosity of not less than 0.381 at 37.8° for the heavy variety, and not more than 0.370 for the light variety. Sp. gr. at 25°, 0.828 to 0.905.

The important test for impurities with sulphuric acid is now carried out with nitrogen-free sulphuric acid, the strength of which is 96%. Probably most chemists have used 98% acid for this test, and the reduction in strength makes a very great difference in the amount of impurity which the test will detect, and the change may lead to a lowering in the standard of purity. Probably the taste is the most important point about the oil, and it is unfortunate that no standard for this quality can be laid down.—N. Evers, *Pharm. J.*, i/1933, 195.

Viscosity of Liquid Paraffin. The introduction of a wider range in sp. gr. in *B.P.* '14 led to the wrong type of "oil" being employed as an intestinal lubricant. An "oil" with a sp. gr. of 0.860 is more of the nature of petrol than liquid paraffin. It passes too rapidly through the system. A light spirit could be positively injurious by reason of its caustic solvent nature. The determination of its viscosity by the Redwood Standard Viscometer—an apparatus devised by the late Sir Boverton Redwood, for the proof of suitability of oils for lubricating

various types of machinery—is therefore of importance. Viscosity is as important as sp. gr., because viscosities may vary when sp. grs. are the same. In a series of liquid paraffins examined by the *Lancet*, viscosities at 100° F. varied from 440 to 67 seconds. The gravity should be as high as possible, at least 0·880, and the viscosity at least 260.

A good mounting medium for bacteria. The refractive index of bacteria is said to be 1·55, canada balsam 1·538, balsam in xylol a little lower, say, 1·53, distilled water 1·336, liquid paraffin 1·471. In a medium exactly that of the bacteria, e.g., oil of aniseed 1·55, the bacteria, dried but unstained, would be invisible, in canada balsam they would be seen, in paraffin better and in water best. Of all practical media Paroleine was found to be best for organisms with flagella. Liquid paraffin is, however, not so good as cedar wood oil for lens immersions.—A. C. Coles, *Lancet*, i/1911, 877.

Paraffinum Liquidum Leve (B.P.C. '34). Sp. gr., 0·835 to 0·850. 50 ml. at 37·8° flows from a Redwood No. 1 viscometer in 60 to 80 seconds. This light liquid paraffin is used as a vehicle for oily spray solutions.

Paraffinum Molle Album (B.P. '32). n_{D60° , 1·453 to 1·460; m.p., 40° to 46°. Volatilises without acrid odour and complies with tests for acidity, fixed oils, soaps and resins. Petrolatum Album, U.S.P. X, complies with the tests for Petrolatum, U.S.P. X.

Paraffinum Molle Flavum (B.P. '32). n_{D60° , 1·460 to 1·474; m.p., 38° to 46°; ash limit, 0·05%. Volatilises without acrid odour, and complies with tests for acidity, fixed oils, soaps and resin. Petrolatum, U.S.P. X, melts between 38° and 54°; sp. gr. at 60°, 0·820 to 0·865; ash, not more than 0·05%.

The lower limit of melting-point of yellow soft paraffin has been lowered from 42° to 38°, and the latter now includes vaseline.—N. Evers, *Pharm. J.*, i/1933, 195.

Petroleum Leve (B.P.C. '34). Not less than 95% distils between 40° and 60°, the sp. gr. of which is 0·620 to 0·700. Residue on evaporation, not more than 0·002% w/v. Benzinum Purificatum, U.S.P. X, has a sp. gr. at 25° of 0·634 to 0·660. Distils completely between 35° and 80°. Residue on evaporation not above 40°, not more than 0·002%.

“Petrol” and Petrol Tests.

Petroleum or Motor Spirit (Gasoline in U.S.A.) This is the lowest boiling commercial fraction of crude petroleum and has, in the U.K., a sp. gr. of about 0·72 to 0·75. The boiling range is from about 35° to about 195°, with approximately 40% distilling at 100°. In the U.S.A. the boiling range is somewhat longer.

Aviation Spirit. A definitely lighter gravity is used with an end point of about 150° to 160°, and is admixed frequently with 20% or more of benzene.

Petrol is a complex mixture of various hydrocarbons mainly saturated and of the paraffin, aromatic and naphthenic types, but at the present time more and more is being obtained by the cracking of the heavier hydrocarbons in petroleum resulting in the formation of cracked gasoline that contains very considerable amounts of the olefine series.

To cope with modern high compression engines, benzene is frequently added to petrol and may be estimated by the increment of sp. gr. it causes and by its effect on the critical solution temperature in aniline.

Coal, and other solid fuels, are converted into liquid fuels (petrol, Diesel oil, and heavy fuel oil) by “**Berginisation**,” a process of hydrogenation under pressure (over 100 atmospheres) at high temperatures (400° to 500°).

Although **gasoline vapour** has an intoxicating effect, the toxicity of a given amount is much less than that of carbon monoxide produced by its incomplete combustion in an engine. Experiments on dogs. The anæsthetic action of gasoline vapour is somewhat like that of ether, but with marked convulsant effects, due doubtless to irritation of the cerebral cortex.—H. W. Haggard, *J. Pharmacol.*, Dec., 1920.

National Benzol Mixture consists of Empire-produced petrol mixed with a variable quantity of coal tar benzol, dependent on the amount of aromatic bodies already present in the petrol, to produce a petrol possessing a high useful compression ratio (h.u.c.r.). The mixture usually contains at least a third of its volume of benzol.

Benzene, Detection in Light Petroleum. A reagent is made by mixing equal volumes of alcohol 95% and aniline. On adding 2 ml. of this to 5 ml.

of light petroleum, the aniline separates and forms a distinctive layer. If it contains 5% of benzene, a perfectly clear solution results. If less than 5% is suspected the petroleum should be fractionated and the test used on the 80° to 110° fraction.—*Yearb. Pharm.*, 1923, 184.

Xylene. British Standard Specifications (B.S.S. No. 458—1932) based on specifications prepared by the National Benzole Association have been issued by the British Standards Institution for xyloles (pure xylene, 3° xylene, and 5° xylene). The requirements control colour, specific gravity, water, distillation range, acid-washing, freedom from acids, alkalis and sulphuretted hydrogen, residue on evaporation, paraffins and sampling, and the appendices describe the methods and apparatus used. Pure xylene has a distillation range for a specified 92% of the liquid of 2.5° between the temperatures of 137.7° and 144°. Similarly 3° xylene has a distillation range of 3°, and 5° xylene has a range of 5° between the same temperatures.

PHENACETINUM

Phenacetinum (B.P. '32). $C_{10}H_{13}O_2N = 179.1$. M.p., 134° to 136°. Ash, not more than 0.05%. Complies with tests for neutrality, readily carbonisable substances, acetanilide and *p*-phenetidine. Acetphenetidinum, U.S.P. X, melts between 134° and 135°. Ash, not more than 0.05%.

Acetanilidum is not included in the B.P. '32, and its purity is controlled by the standard of the B.P.C. '34. It is also official in the U.S.P. X.

Estimation. Hydrolyse 1.5 g. by boiling for 15 minutes with 50 ml. of 20% hydrochloric acid and dilute to 500 ml. To 25 ml. of this solution add excess standard potassium bromide-bromate solution to precipitate tribromoaniline, and estimate excess bromine in the usual way.—*J. chem. Soc. Abstr.*, ii/1921, 604.

Tentative quantitative methods for the determination of Acetanilide, Phenacetin and Caffeine in tablets are described in Methods of Analysis (A.O.A.C., 1930, 439 and 444).

Toxicology. Danger of acetanilide in headache powders.—Dixon, *Pharm. J.*, ii/1912, 555.

Toxicological studies of acetanilide poisoning.—A. G. Young and J. A. Wilson, *J. Pharmacol.*, Mar. 1926, 133.

Chronic acetanilide poisoning. Increasingly large doses taken daily over a period of 20 years, with an ultimate daily intake of 8.4 g. (in the form of 200 g. of "Bromoseltzer"). Marked cyanosis the most striking feature on admission to hospital. Recovery 2 months after withdrawal of drug.—L. C. Fisher, *J. Amer. med. Ass.*, i/1933, 737.

Addiction from 60 grains daily.—*Pharm. J.*, ii/1933, 37.

Effect of other drugs on toxicity of acetanilide. Sodium bicarbonate has power in combating its toxic effects. The toxicity of acetanilide is increased by caffeine, codeine and morphine.

PHENAZONUM

Phenazonum (B.P. '32). $C_{11}H_{12}ON_2 = 188.1$. M.p., 111° to 113°. Ash, not more than 0.1%. Antipyrina, U.S.P. X, leaves not more than 0.1% of ash.

Determination. It may be precipitated as $(C_{11}H_{12}N_2O)_2, H_4Fe(CN)_6$ from an acid solution by means of potassium ferrocyanide. A weighed quantity of the sample, containing 0.2 to 0.3 g. of phenazone, dissolved in 30 ml. of 0.8N HCl is treated with 20 ml. of M/2 potassium ferrocyanide added slowly with stirring. Allow to stand for 30 minutes, collect in a Gooch crucible, wash with saturated aqueous phenazone hydroferrocyanide and dry at 105° to 110°. Add a correction of 0.005 g. for solubility. The precipitate contains 63.53% of phenazone. A

volumetric method for determining the precipitate is also described. Amidopyrine does not interfere with either result.—I. M. Kolthoff, *J. Amer. pharm. Ass.*, 1933, 22, 947.

0.2 g. of the antipyrine and 2 g. of sodium acetate are dissolved in 20 ml. of water in a stoppered flask and 30 ml. of N/10 iodine solution added. The flask and contents are allowed to stand with occasional shaking for 20 minutes. The precipitate is then dissolved by adding 10 ml. of chloroform and shaking, and the excess of iodine titrated with N/10 sodium thiosulphate solution. The amount of iodine reacting with the reagents is determined by repeating the process, omitting the antipyrine, or preferably by using only 10 ml. of N/10 iodine for the blank determination. An allowance is made for the iodine which reacts with the reagents.—H. Brindle, *Quart. J. Pharm.*, 1934, 453.

Phenazoni Salicylas (*B.P.C.* '34). $C_{11}H_{12}ON_2, C_7H_6O_3 = 326.2$. Contains not less than 57% of phenazone, and not less than 42% of salicylic acid. M.p., 91° to 92°. Ash limit, 0.1%. Assayed for phenazone by extraction with chloroform from sodium hydroxide; the residue on evaporation responds to the identity tests for Phenazonum. Salicylic acid content is determined by titration in 60% alcohol solution with N/10 sodium hydroxide to phenol red.

Antipyrinum salicylicum, *P. Helv. V*, contains 42.0% to 42.3% of salicylic acid when a solution of 1 g. in 20 ml. of alcohol and 30 ml. of water is titrated with N/10 sodium hydroxide, using phenolphthalein as indicator.

Amidopyrina (*B.P.* '32). $C_{13}H_{17}ON_3 = 231.2$. M.p., 107° to 109°. Ash limit, 0.1%.

PHENOL

Phenol (*B.P.* '32). $C_6H_6O = 94.05$. Contains not less than 98% of the pure substance. Residue on volatilisation on a water-bath, not more than 0.05%. Assayed for bromine absorption by a modified Koppeschaar process (*vide infra*).

The following *British Standard Specifications* have been prepared by the British Standards Institution for different grades of phenol and carbolic acids. Each specification contains descriptions in detail of the tests which are applied and descriptions of the apparatus used.

B.S.S. No. 523—1933 relates to crystalline phenol and liquefied phenol or solutions of phenol.

B.S.S. No. 516A—1933 and *No. 516B—1933* cover distilled carbolic acids 60's and distilled carbolic acids 45's respectively containing less than 3% of water. The former has a specific gravity not lower than 1.055 at 15.5°, and a crystallising point not lower than 60°F., whilst the latter has a sp. gr. not lower than 1.050 at 15.5° and a crystallising point not lower than 45°F.

B.S.S. No. 515A—1933 and *No. 515B—1933* refer to crude carbolic acids, 60's and 45's. Crude carbolic acid 60's contains not more than 15% of water, has a gravity not lower than 1.055 and shows not more than 6% of residue on distillation, whilst crude carbolic acid 45's contains not more than 12% of water, has a gravity not lower than 1.050 and shows also not more than 6% of residue on distillation.

Quantitative Estimation of Phenol, Koppeschaar Process. This depends upon converting it into tribromophenol, $C_6H_2Br_3OH$:—

Dissolve phenol, 1.5 g., in water sufficient to make 1000 ml. Place 25 ml. of the solution in a 200 ml. stoppered bottle, add 30 ml. of N/10 bromine solution (**Koppeschaar's Solution**) and shake repeatedly for half an hour; allow to stand 15 minutes then add 5 ml. of 10% potassium iodide solution, shake well, add 1 ml. of chloroform and titrate excess of iodine with N/10 thiosulphate. Subtract the number of ml. required from thirty; the remainder equals the number of ml. of N/10 bromine used up. This multiplied by 4 gives the percentage of absolute phenol (i.e. 1 ml. N/10 Br = 0.001568 g. of phenol).

Koppeschaar's Bromine Solution is made as follows:—

Dissolve potassium bromate, 3.2 g., and potassium bromide, 50 g., in water, 900 ml. To standardise, place 20 ml. in a 250 ml. bottle with 75 ml. of water and 5 ml. of hydrochloric acid. Shake a few times, quickly introduce 5 ml. of 20% potassium iodide solution and titrate the iodine set free with N/10 sodium thiosulphate. Dilute the bromine solution so that equal volumes of it and the

N/10 thiosulphate exactly correspond in the conditions of the test.—*cf.* *U.S.P. X*, p. 498 and *B.P. '32*, p. 513.

Phenol Liquefactum (*B.P. '32*). Contains 78.5% to 81.5% *w/w* of phenol. The *U.S.P. X* preparation contains not less than 88% *w/w* of C_6H_5OH .

Inhalation of fumes of carbolic acid, owing to dropping of a winchester and the boy starting to mop it up with a cloth, caused grave poisoning symptoms. Intravenous saline, 2 pints, with addition of 2 drachms of sodium bicarbonate saved life. Breathing (assisted by the use of oxygen) improved at once.—R. Eccles Smith, *Lancet*, ii/1922, 1359.

Absorption of crude carbolic acid through the skin with fatal result. A bottle of carbolic acid in a man's pocket on his journey home by train—extensive burning of arm, thigh and scrotum. Ultimate death.—W. R. M. Turtle and T. Dolan, *Lancet*, ii/1922, 1273.

Trochiscus Phenolis. *Assay.* For the assay of phenol in preparations containing ingredients which react with bromine a known quantity of the preparation containing about 0.15 g. of phenol is placed in a flask with 125 ml. of water, acidified with hydrochloric acid, and 25 g. of anhydrous calcium chloride added. The mixture is distilled until about 100 ml. of distillate is collected. The volume of distillate is adjusted exactly to 100 ml. and the phenol determined in 30 to 40 ml. of the solution by the *B.P.* method. In the case of phenol lozenges, allowance should be made for loss of phenol during manufacture. The standard should be set on the percentage of phenol present and not on the amount in each lozenge. The lozenges should be required to weigh not less than 1.10 and not more than 1.22 g., and contain not less than 1.75% of C_6H_5OH .—C. E. Corfield and L. M. Mundy, *Quart. J. Pharm.*, 1932, 504.

The following is an alternative process:—The lozenges are first weighed, and crushed. A convenient weight of the crushed material, usually about 3 to 4 g., is dissolved in water, and the solution adjusted to a volume of 100 ml. 25 ml. of this solution is placed in a 300 ml. flask, and diluted with water to a volume of 50 ml. The flask is fitted to a condenser, and the contents distilled until only about 5 ml. remain in the flask. An asbestos ring should be used to prevent overheating. Distillation may be rapid at first, but towards the end, caution is required to prevent overheating and possible charring of the residue. The distillate is collected in a 300 ml. stoppered bottle, and the temperature brought to about 20°. 30 ml. of N/10 iodine and 30 ml. of N/10 sodium carbonate are added, and the mixture allowed to stand for 5 minutes. The mixture is then acidified by the addition of 5 ml. of dilute sulphuric acid, and the excess iodine is titrated with N/10 sodium thiosulphate. Each millilitre of N/10 iodine is equivalent to 0.001567 g. of phenol.—C. A. Hill and A. D. Powell, *Quart. J. Pharm.*, 1934, 535.

Unguentum Phenolis. *Assay.* The phenol may be separated from the base in a form suitable for titration with bromine either by distillation from acid solution or by solution in N/1 sodium hydroxide and separation of the phenol solution by means of calcium chloride.—E. M. Smelt, *Quart. J. Pharm.*, 1932, 509.

Betanaphthol (*B.P. '32*). $C_{10}H_8O = 144.1$. M.p., 120° to 122°. Ash, not more than 0.05%. No violet colour should be produced when the precipitate produced by ferric chloride is heated.

Hexyl-Resorcinol (*B.P.C. '34*). $C_{12}H_{18}O_2 = 194.1$. M.p., not below 66°. Ash, not more than 0.1%.

Pyrogallol (*B.P.C. '34*). $C_6H_6O_3 = 126.0$. M.p., 129° to 135°. Ash limit, 0.1%. The aqueous solution is clear, not more than slightly yellow, and neutral to methyl orange.

Resorcinol (*B.P. '32*). $C_6H_6O_2 = 110.0$. M.p., 110° to 111°. Ash limit, 0.05%. A 5% solution produces no precipitate with lead acetate solution, indicating absence of catechol. Resorcinol, *U.S.P. X*, after drying to constant weight over sulphuric acid, contains not less than 99.5% of $C_6H_4(OH)_2$. Assayed by bromine absorption during 1 minute, interaction with potassium iodide and titration with N/10 sodium thiosulphate.

Sodii Phenolsulphonas (*B.P.C. '34*). $C_6H_5O_4SNa, 2H_2O = 232.1$. Assayed on its power of bromine absorption it contains from 99% to the equivalent of 103% of the pure substance.

Trinitrophenol (*B.P. '32*). $C_6H_3O_7N_3 = 229.0$. Contains not less than 99% of $C_6H_3O_7N_3$. M.p., 121° to 123° (precautions being taken). Residue on extraction with benzene at 50°, not more than 0.1%. Determined by titration

with sodium hydroxide to phenolphthalein. The *U.S.P. X* allows 0.2% matter insoluble in benzene at ordinary temperature and dried at 100°. Acidic picricum, *P. Helv. V*, is assayed by dissolving 0.29 g. in 30 ml. of water and adding 10 ml. of a solution containing 0.36% of potassium iodate and 1.5% potassium iodide. When the potassium picrate formed has dissolved, titrate with N/10 sodium thiosulphate, using starch as indicator towards the end of the titration and making a blank on the iodate-iodide solution. 1 ml. of N/10 $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ is equivalent to 0.022905 g. of $\text{C}_6\text{H}_3\text{O}_7\text{N}_3$.

If confined, trinitrophenol (picric acid) explodes somewhat more readily than ammonium picrate, but with slightly less vigour, when heated in a test-tube. Trinitrophenol does not explode on striking with a hammer on an iron plate. As a high explosive it is used in shells, e.g., as **Lyddite**, **melinite**, etc., etc. It is safe, i.e., it is sufficiently insensitive to shock to prevent it from being exploded when struck by projectiles or fired from a gun. T.N.T. is less sensitive to shock than trinitrophenol, and is unaffected by water and metals.

Eugene Turpin in 1885 discovered that, provided the initial ignition is of sufficient violence, pure picric acid is one of the most powerful explosives. He also showed that the substance could be poured in a molten condition or be pressed in to shells or grenades. Turpin's Shell, which is essentially the same as modern high explosive shell, comprises the shell body filled with the acid, the point of the shell containing priming which is exploded by means of a percussion detonator. As the m.p. of the substance is somewhat high, and this is inconvenient for working, various additions have been made to lower the melting-point, e.g. nitro-naphthalene, camphor, T.N.T., etc. Various names have been adopted, e.g., melinite, lyddite, schimose (Japanese), etc.

Many accidents have occurred in its manufacture and filling—generally attributed to contact with metal oxides, chalk, brickwork, etc., and hence the formation of salts, the intermediate formation of these picrates resulting in the detonation of the acid. Picric acid has been largely displaced by T.N.T.—From *High Explosives*, by E. de W. S. Colver, 1918.

A solution precipitates most alkaloids cf. *Scheme for Recognition of Organic Chemicals*.

Carbasus Trinitrophenolis (*B.P.C.* '34). By titration of the gauze shaken with water a content of from 1.5% to 2.5% *w/w* of $\text{C}_6\text{H}_3\text{O}_7\text{N}_3$ should be indicated.

"T.N.T." Trinitrotoluene. Syn. Trotyl. $\text{C}_6\text{H}_2\text{CH}_3(\text{NO}_2)_3 = 227.06$. Commercially it is seen as crumbs or granules of fine plate crystals. Melting-point about 80°. It is obtained by nitrating toluene. Soluble in acetone, ether, benzene, and xylol.

As an explosive it has replaced picric acid. "T.N.T." is more stable and does not attack metals. When absorbed, mainly through the skin, it leads to serious digestive trouble. It further induces hæmolysis and cyanosis. The brunt of the mischief falls on the liver.

Stomonal consists approximately of nitroglycerin 11, ammonium nitrate 57½, sodium nitrate 7, sodium chloride 20½, wheat flour 8½, moisture 1.

AMATOL is T.N.T. mixed with 40% to 60% of ammonium nitrate. Mixed with 20% it is AMMONAL.

T.N.T. and "Stomonal" dermatitis. A pigment of camphor 2 drachms, phenol 1½ drachms, mercuric chloride 15 grains, picric acid ½ drachm and alcohol 6 ozs. 6 drachms is useful. Dabbed on by the medical man freely—never given to the patient—on inflamed and itching parts (not on irritable mucous surfaces). Especially valuable in the early pruriginous stages. For home use 2 ozs. of the pigment mixed with a calamine lotion 4 ozs. and ½ drachm of acacia gum added.—K. Prosser White, *Lancet*, i/1916, 402; see also A. Livingstone, Learmouth and B. M. Cunningham, *Lancet*, ii/1916, 261.

Ministry of Munitions on T.N.T. and poisoning. It produced 50 cases of fatal toxic jaundice out of many thousands of workers engaged. Account of dermatitis, digestive troubles, blood changes, and jaundice caused.—*Brit. med. J.*, ii/1916, 842; *Lancet*, ii/1916, 1026.

Sodium bicarbonate freely given; successful treatment.—*Brit. med. J.*, i/1916, 450.

Effect on the blood. No adverse effect on the red cells and hæmoglobin. Appreciable increase in leucocytes. Cyanosis is common among workers, possibly production of NO-hæmoglobin or methæmoglobin—P. N. Pantley, *Lancet*, ii/1917, 77.

Three grains in 1 grain doses taken experimentally. Urine becomes orange colour.—Walter Smith, *Brit. med. J.*, i/1917, 618.

Tests for T.N.T. In the free state a weak ethereal solution gives a deep red with caustic potash—preferably in alcoholic solution.

WEBSTER'S TEST for detection in the urine. 12.5 ml. of the urine mixed with an equal volume of sulphuric acid (20 : 100) and shaken with 10 ml. of ether. The acid liquor is rejected and the ether washed once with 25 ml. of water. When treated this ether solution with 5 ml. of alcoholic potash solution (4 or 5 : 100) when T.N.T. is present a purple colour is at once formed varying in intensity. Care must be taken to distinguish between absorbed T.N.T. and accidental contamination.—B. Moore, *Med. Pr.*, 1916, 153, 647. See also *Brit. med. J.*, i/1917, 618 and especially *Lancet*, ii/1916, 1029. Also modification to exclude possible errors through consumption of rhubarb, etc.—F. Tutin, *Lancet*, i/1918, 554.

T.N.T. poisoning—how it was tracked and prevented.—B. Moore, *Brit. med. J.*, ii/1921, 721.

For further information on T.N.T. and other explosives see "High Explosives" by E. de W. S. Colver, 1918; "T.N.T. and Mono- and Di-Nitrotoluene, their manufacture and properties."—G. Carlton Smith, 1918; and "Explosives," by E. de Barry Barnett, 1919.

TRINITRO-BUTYL-TOLUENE, $C_8HCH_3C_4H_9(NO_2)_3$ is synthetic musk or tonalol, referred to in Vol. I, pp. 395, 868.

In artificial musks, it is possible to replace the nitro groups by CHO, OCH_3 , OC_2H_5 , halogens and CN, without altering the odour, but the tertiary butyl group, or the presence of tertiary carbon, is essential.—*Perfum. essent. Oil. Rec.*, 1924, 360.

PHENOLPHTHALEINUM

Phenolphthaleinum (*B.P.* '32). $C_{20}H_{14}O_4 = 318.1$. M.p., 54° to 258° . Sulphated ash, not more than 0.05%. The *U.S.P.* X requires the m.p. to be not below 256° ; ash, not more than 0.05%.

The upper limit of the *B.P.* melting-point range is too low. The majority of commercial samples have a melting-point of about 260° .

An official quantitative method for the determination of Phenolphthalein in tablets is described in *Methods of Analysis (A.O.A.C., 1930, 466)*.

Fluoresceinum Solubile (*B.P.* '32). $C_{20}H_{10}O_5Na_2 = 376.1$. Soluble fluorescein loses at 105° not more than 5%.

Iodophthaleinum (*B.P.* '32). $C_{20}H_8O_4I_4Na_2, 3H_2O = 919.8$. Contains not less than 85% of phthalein, and the separated phthalein contains 61% to 62% of I. Assayed by precipitation of the phthalein from aqueous solution with dilute hydrochloric acid, washing with a mixture of equal volumes of acid and water, and drying at 110° ; by fusion of a portion of the residue with sodium carbonate, extraction with hydrochloric acid and water, and titration with M/20 potassium iodate the iodine content is obtained.

The use of this compound as a diagnostic test for cholecystic disease is described in Vol. I, p. 675, and this Vol. p. 703.

Phenol-Rubrum (*B.P.C.* '34). $C_{19}H_{14}O_5S = 354.2$. Phenol red loses at 110° , not more than 1%. Sulphated ash, not more than 0.2%.

Phenolsulphonaphthalein (Phenol red) Test for Hydrocephalus. Puncture one or other lateral ventricle and withdraw 1 or 2 ml. of cerebrospinal fluid into a syringe containing 1 ml. phenolsulphonaphthalein solution as used for kidney test (*q.v.*). Inject mixture into ventricle and withdraw needle. After an interval perform lumbar puncture and allow spinal fluid to pass into a test-tube containing a few drops of 25% sodium hydroxide solution; repeat in 30 minutes. Recovery of indicator (pink colouration of spinal fluid on contact with sodium hydroxide) shows existence of hydrocephalus not due to intraventricular obstruction up to and including point of exit of the fluid from the fourth ventricle, i.e., it shows an extra-ventricular hydrocephalus: non-recovery of indicator shows intra-ventricular hydrocephalus.

Another test not so frequently used is the recovery of the ventricular injection substance from the urine. If ventricular hydrocephalus exists none of the

indicator is recoverable within 2 hours: if an extra-ventricular hydrocephalus is present the indicator will be recoverable, but not as in a normal case. Technique more difficult and knowledge afforded similar to that of the simpler method.—Fraser's *Surgery of Childhood*, 1926, p. 496.

For the use of phenol red as a renal function test see p. 330.

PIPER NIGRUM

Piper Nigrum (B.P.C. '34). Contains not more than 2% of foreign organic matter. Ash, not more than 6%. Acid-insoluble ash, not more than 1%. Piper, N.F. V, contains not more than 2% of stems or other foreign matter.

The Food and Drug Administration of the U.S. Dept. of Agriculture defines black pepper as the dried immature berry of *Piper nigrum* L. Contains not less than 6.75% of non-volatile ether extract, not less than 30% of starch, not more than 7% of total ash and not more than 1.5% of ash insoluble in hydrochloric acid. **Ground black pepper**: the product made by grinding the entire berry of *Piper nigrum* L.; contains the several parts of the berry in their normal proportions. **Long pepper**: the dried fruit of *Piper longum* L. **White pepper**: the dried mature berry of *Piper nigrum* L. less the outer, or outer and inner, coatings. Contains not less than 7% of non-volatile ether extract, not less than 52% of starch, not more than 5% of crude fibre, not more than 3.5% of total ash, and not more than 0.3% of ash insoluble in hydrochloric acid.—S. R. A., F.D. No. 2, Rev. 4, Aug. 1933.

Cubeba (B.P.C. '34). Should contain not more than 7% of shrivelled immature fruits, rachis and stems, and not more than 2% of foreign organic matter. Ash limit, 8%. Cubeba, U.S.P. X, should yield not less than 10% of volatile ether-soluble extractive; shrivelled fruits or stems, not more than 5% foreign organic matter, not more than 2%.

Oleum Cubebæ (B.P.C. '34). Sp. gr., 0.910 to 0.930; α_D^{20} , -20° to 35° ; n_{D20} , 1.480 to 1.502. Not less than 60% distils between 250° and 280° .

PIX CARBONIS

Pix Carbonis (B.P.C. '34). Ash, not more than 2%. Water shaken with it gives an alkaline reaction.

Pix Carbonis Præparata (B.P. '32). Coal tar heated at 50° for one hour.

Pix Liquida (B.P. '32). Wood tar, known in commerce as Stockholm tar. Pix Pini, U.S.P. X, leaves not more than 0.25% of ash.

Stockholm Tar is a peasant-made article; this tar can be separated by fractional distillation into three principal fractions: (1) A watery portion containing pyroligneous acid, methyl alcohol or wood naphtha, and acetone. (2) **light oil of tar** which contains some of these substances, toluol, xylol, and other hydrocarbons of that series; and (3) **heavy oil of tar** which contains phenols, creosol and guaiacol. The redistillation residue is ordinary block pitch. It has been arranged to define wood tar made by burning the roots of the Swedish pine tree (*P. sylvestris*) in the peasant way—so-called "**Dalbrand tar**" as "genuine Swedish peasant-made tar" and that "Factory tar" of Swedish origin shall in future be called "*Swedish kiln tar*."—*Chem. & Drugg.*, ii/1913, 331. See also D. McEwan, *Chem. & Drugg.*, i/1911, 264.

Rectified Oil of Tar. One gallon of Stockholm tar yielded only a few ounces of oil with sp. gr. 0.921, but American wood tar oil yielded nearly 40% of a brown oil with characteristic tar odour, having sp. gr. 0.920. This redistilled with soda gave a colourless oil with faint terebene odour and sp. gr. 0.881 and flash-point 124°F . Commercially it is made from imported tar oil from Russia, Sweden and America by distilling and refining here.—E. J. Millard, *Pharm. J.*, i/1918, 28.

Oleum Cadinum (B.P. '32). Sp. gr., 0.975 to 1.010; n_{D20} , 1.510 to 1.530. The presence of pine tar oil is excluded by the absence of green colour in the resin test when a petroleum extract is shaken with copper acetate solution.

eum Cadinum, *U.S.P. X*, should also comply with this test for rosin or rosin
s and has a sp. gr. at 25° of 0.980 to 1.055..
For the method of production of crude oil, see Pepin, *Yearb. Pharm.*, 1907, 27.
The author states that the copper acetate test will detect the addition of 10%
pine tar oil. Martindale was, however, unable to detect less than 20%
dition.

PLUMBUM

Plumbi Acetas (*B.P. '32*). $C_4H_6O_4Pb, 3H_2O = 379.3$. Con-
sins from 99.5% to the equivalent of 104.5% of the pure substance.
ssayed by precipitation as oxalate and titration with N/10
potassium permanganate. Plumbi Acetas, *U.S.P. X*, contains
5.31% to 89.57% of the anhydrous salt, corresponding to not less
than 99.5% of the trihydrate.

In the *B.P.* test for absence of copper, etc., 2 ml. of dilute sulphuric acid
ould be used, since the 1 ml. specified is insufficient to precipitate the whole
f the lead.

Plumbi Carbonas (*B.P.C. '34*). Assayed for lead content by precipitation
f the acetic acid solution with ammonium oxalate and titration of the precipitate,
ecomposed by sulphuric acid, with N/10 potassium permanganate, not less
than 79% of Pb should be indicated. Matter insoluble in diluted nitric acid, not
more than 1%.

Plumbi Iodidum (*B.P.C. '34*). $PbI_2 = 461.1$. Assayed for halogen content
y addition of excess silver nitrate and nitric acid to a solution in sodium
ydroxide solution, and back titration with N/10 ammonium thiocyanate; after
allowance for the chloride in the sodium hydroxide solution, a purity of not
ess than 95% is required. Plumbi Iodidum, *N.F.V.*, after drying over sulphuric
cid for 24 hours, contains not less than 99% of PbI_2 .

Plumbi Monoxidum (*B.P. '32*). $PbO = 223.2$. Loses not more than 4%
n ignition and then contains not less than 99% of PbO. Assayed by precipita-
ion as oxalate and titration with N/10 potassium permanganate. Plumbi
Monoxidum, *U.S.P. X*, is assayed by precipitation with excess N/10 oxalic
cid, filtration and titration of the excess acid in an aliquot part with N/10
potassium permanganate; a purity of the freshly ignited substance of not less
than 97% is required.

The B.P. '32 methods for the assay of lead preparations are inaccurate.
Alternative methods of assay, which combine sufficient accuracy with easy and
apid manipulation, are suggested, and also assay processes for the suppository
and plaster.—S. Wetherell, *Quart. J. Pharm.*, 1935, No. 3.

LEAD POISONING

Lead Paint Regulations 1927 (S.R. & O., 1927, No. 847), under Lead Paint
Protection against Poisoning) Act 1926 (16 and 17 Geo. 5, c. 37).

Lead paint for buildings must be in paste form or paint ready for use (but
ed lead may be had raw or dry for stopping or filling). Must not be used in
orm of spray in interiors. Surfaces other than iron or steel must not be rubbed
down or scraped by dry process, except if the surface contains no lead.

Spraying Paint or Lacquer. The practice of spraying paints or lacquer
containing over 1% of lead should be discontinued, or carried out only where
adequate air movement is provided. Similarly, the amount of benzol used
n lacquers should be limited to 0.5%. Definite silicosis hazard from spraying
of vitreous enamels.—*Lancet*, ii/1928, 177.

English Potteries, Lead Poisoning in. Home Office Report.—*Brit. med. J.*,
i/1911, 44.

BEER. Cases at Isleworth due to lead glaze enamel on iron tanks; 93 persons
affected.—*Med. Pr.*, Oct. 4th, 1922, 295.

CIDER. An outbreak of lead colic in Devonshire among cider-drinkers due to
lead conducting pipes, used to draw the cider from the cask to the engine.
Owing to its greater acidity, cider is a more active solvent of lead than beer.—
M. C. N. Jackson and L. N. Jackson, *Lancet*, ii/1932, 717.

SNUFF wrapped in tinfoil caused three cases of chronic poisoning.—J. Uttal,
J. Amer. med. Ass., i/1928, 290.

DISTRIBUTION AND STORAGE OF LEAD IN THE ORGANISM. It has been shown that lead is retained indefinitely in the solid portion of the bones. Such lead is harmless, but is held at a point where its liberation would flood the organism with toxic soluble lead. A depleted alkali reserve tends to mobilise the stored lead.—A. S. Minot and J. C. Aub, *J. Pharmacol.*, March 1924, 159.

Lead is absorbed most easily through the respiratory tract, and as little as 1 to 2 mg. daily is likely to produce chronic poisoning. It may be stored in the skeleton or eliminated by excretion, and may be carried in the blood stream as colloidal lead phosphate and deposited as tertiary lead phosphate. When lead is generally distributed throughout the organism it is desirable to facilitate storage with an ample calcium intake. After acute toxic symptoms have passed elimination is helped by low calcium intake. A danger exists in the use of containers glazed or soldered with lead compounds.—*J. Amer. med. Ass.*, ii/1928, 2034.

A Test for Lead Absorption. In normal persons the number of basophilic cells per ml. of blood is as a rule less than 1000 and never exceeds 5000. Lead poisoning produces counts over 7000 and up to 100,000, but symptoms may not occur even when the count is as high as 60,000 to 80,000. When a worker who is exposed to lead develops a basophilic red cell count over 6000 or 7000 and when other conditions which might produce such a count are absent (certain physiologic states—benzene poisoning, arsenic poisoning, all types of anæmia in which there is regeneration, hæmolytic icterus, the condition following hæmorrhage, leukæmias, acute infections, neoplasms involving bone marrow and polycythæmia—) increase the proportion of basophilic cells up to 20,000 the worker should be considered a lead poisoning prospect.—*J. Amer. med. Ass.*, ii/1928, 251.

Lead poisoning included in France, in October, 1919, among the liabilities of employers' and workmen's compensation insurance agencies. As a result of the examination of 179 workers—apparently healthy—exposed to lead poisoning, the lead line was found in 65%. The LEAD LINE is not a uniform or reliable sign of lead poisoning. Early and accurate information can only be obtained by demonstration of lead in the urine and basophil granules in the red corpuscles.—A. Feil and R. Heim de Balsac, per *Lancet*, i/1923, 132.

No diagnostic value in qualitative lead determinations in urine or fæces. In most persons have absorbed appreciable quantities. There is no quantitative expression of lead secretion in man significant of impending or present lead poisoning.—R. A. Kehoe and co-workers, *J. Amer. med. Ass.*, ii/1928, 2084.

The individual American ingests from $\frac{1}{8}$ to $\frac{1}{4}$ mg. of lead per day, and excretes approximately the same quantity at the rate of 0.02 to 0.08 mg. per litre of urine and 0.03 to 0.1 mg. per gramme ash of fæces. The mere presence of lead in the excreta of a worker possesses no diagnostic significance. If the average lead hazard of a trade results in a mean daily fæcal output of lead in excess of 1.1 mg. and a mean urinary excretion of lead in excess of 0.21 mg. per litre, cases of lead poisoning may be expected to occur, but for the individual case diagnosis must continue to rest largely on clinical evidence.—*Brit. med. J.*, i/1934, 766.

The determination of traces of lead in bone and biological materials can be made without ashing the organic material by the use of diphenylthiocarbazide to extract the lead. Fresh bone contains from 14.5 to 146 parts per million of lead; teeth from five normal persons contained 42.5 to 247.5 parts per million.—G. Roche Lynch, R. H. Slater and T. G. Osler, *Analyst*, 1934, 787.

Lead Tetraethyl is a liquid boiling at 150° with decomposition. It is manufactured by treating lead tetrachloride with methyl magnesium iodide. The products of combustion are: (1) with excess air—chiefly carbon dioxide and lead oxide, (2) with deficiency of air (e.g., in engine cylinder)—chiefly carbon monoxide and lead. It is not very volatile at ordinary temperatures.—*Pharm. J.*, i/1928, 268. For further data see Vol. I, p. 656.

Lead poisoning due to the manufacture, etc., of tetraethyl lead. The condition bears little resemblance to clinical types of lead poisoning. The compound is not immediately corrosive, but causes necrosis after lengthy exposure. If allowed to remain on the skin for half an hour no sensation is produced, but desquamation occurs after a day or two. Poisoning results from a combination of skin absorption and inhalation of vapour. The inhalation of dust has also caused illness.—R. A. Kehoe, *J. Amer. med. Ass.*, ii/1925, 108.

Post-mortem findings in 4 cases of poisoning. A volatile lead compound was proved in the brain tissue. All the organs, including the blood, contained lead.—C. Norris and A. O. Gettler, *J. Amer. med. Ass.*, ii/1925, 820.

Determination in motor fuels of lead tetraethyl.—*Analyst*, 1926, 104.

Ethyl petrol coming into this country from the U.S.A. contains 6 ml. of ethyl lead per gallon. The **ethyl fluid** consists of lead tetraethyl 54.5%, ethylene bromide 36.5%, monochloronaphthalene 9%, with a trace of Sudan IV.—*Nature*, Lond., 1928, 424.

Interim Report of Departmental Committee of Min. Health (Report issued July 27th, 1928). There is no evidence that the use of ethyl petrol involves more danger to health than the ordinary, but the precautions suggested by the S. Committee should be carried out, e.g., labelling of cans and pumps, affixing of labels, and dyeing of the substance red. Warning against use for purposes other than as motor fuel, e.g., cooking and cleaning. In no case does the amount of lead tetraethyl in commercial spirit exceed 1 in 1300 by volume or 1 in 650 by weight. The deaths in the U.S.A. not attributed to the diluted mixture (ethyl petrol). Drivers and garage employees in U.S.A. gave no definite signs of poisoning after exposure for 2 years.—*Brit. med. J.*, ii/1928, 219.

In view of the difficulty of recognising poisoning by lead ethyl, we should protest against the use of ethyl petrol. Are we to put a higher value on a slightly increased efficiency of engines than on a certain, even if slight, impairment of the health, efficiency and longevity of our exquisite bodily machinery?—F. C. Mott, *Brit. med. J.*, ii/1928, 222.

PODOPHYLLUM

Podophyllum (B.P. '32). Contains not more than 2% of other organic matter. Podophyllum, *U.S.P. X*, yields not less than 3% of resin of podophyllum; assayed by continuous extraction, followed by percolation and adjustment to volume with alcohol; an aliquot part is mixed with a half volume of chloroform and a volume of saturated potassium citrate solution, shaken and stood overnight; the filtered alcohol-chloroform liquid and washings are evaporated to dryness and dried at 100°.

The *U.S.P. X* assay process gives a final product contaminated with potassium citrate. The following is suggested:—Reflux 10 g. of drug, in No. 60 powder with 60 ml. of alcohol for 3 hours. Transfer to a percolator and percolate with warm alcohol until 95 ml. is collected; cool and make up to 100 ml. Transfer 10 ml. of liquid to a separator, add 10 ml. of chloroform and 10 ml. of 0.6% hydrochloric acid. Shake, allow to separate, and wash the acid layer three times with 15 ml. portions of alcohol-chloroform mixture (1 : 2), adding the washings to the second separator. Add 10 ml. of 0.6% hydrochloric acid to the combined extract and washings, shake, and draw off the alcohol-chloroform layer into a tared vessel. Wash the acid layer three times with 15 ml. portions of the alcohol-chloroform mixture, adding the washings to the tared vessel. Evaporate to dryness, add 1 ml. of dehydrated alcohol and dry to constant weight at 100°.—C. N. Sprinkle and C. B. Jordan, *J. Amer. pharm. Ass.*, 1932, 188.

Podophyllum Indicum (B.P. '32). Contains not more than 2% of foreign organic matter.

T. A. Henry found that the action of both podophyllum and Indian podophyllum is due to podophyllotoxin (purgative) and podophylloresin (purgative and cholagogue). The Indian is richer in the former.

Podophylli Resina (B.P. '32). Loss at 100°, not more than 5%. Ash, not more than 1%. Matter insoluble in dilute solution of ammonia, not more than 10% for resin from podophyllum, and not more than 50% for resin from Indian podophyllum. Resina Podophylli, *U.S.P. X*, is obtained from *Podophyllum peltatum* only; ash, not more than 1.5%; yields not less than 75% of matter insoluble in ether and dried at 100°, and not less than 65% to chloroform and dried at 100°. Podophyllum, *P. Helv. V*, is the mixture obtained by precipitation with water from an alcoholic extract of the rhizome of *Podophyllum peltatum*.

containing not less than 40% of podophyllotoxin. *Assay*. Shake frequently during 30 minutes 0.45 g. in fine powder with 15 ml. of chloroform; transfer 10 ml. of the filtered solution (=0.3 g. of the drug) to a tared flask with 50 g. of light petroleum, collect the precipitate on a tared filter and wash the flask and filter with 20 ml. of light petroleum. Dry the flask and filter with the precipitate for 1 hour at 70° and weigh. The dried residue should weigh not less than 0.12 g.

The resin from *P. emodi* is distinguished from that obtained from *P. peltatum* by the following test:—Podophyllin resin, 0.4 g., is mixed with alcohol 60% 3 ml., and N/1 potassium hydroxide 0.5 to 1 ml. added. Gelatinisation occurs with *P. emodi* only.—*U.S.P. X* modified by D. B. Dott, *Quart. J. Pharm.* 1928, 266.

POTASSIUM AND SODIUM

Potassii Bicarbonas (*B.P.* '32). $\text{KHCO}_3 = 100.1$. Contains from 99% to the equivalent of 100.5% of KHCO_3 . The *U.S.P. X* substance should contain not less than 99% of KHCO_3 , after drying over sulphuric acid.

Potassii Carbonas (*B.P.* '32). Loses from 14% to 18% when dried at 200° to 300°, and then contains not less than 99% of K_2CO_3 . Potassii Carbonas *U.S.P. X*, dried to constant weight at 180°, contains not less than 99% of K_2CO_3 . Loss at 180°, not more than 15%.

Potassii Chloras (*B.P.* '32). $\text{KClO}_3 = 122.6$. Contains not less than 99% of the pure salt. Assayed by digestion, for 20 minutes at 50°, of a solution with acid ferrous sulphate solution and potassium iodide, followed by dilution and titration of the liberated iodine with N/10 sodium thiosulphate, a blank titration being made. The *U.S.P. X* assays by reducing a solution with acid ferrous sulphate solution by boiling for 10 minutes, manganous sulphate solution is added and the excess ferrous sulphate titrated with N/10 potassium permanganate, a blank determination being performed; a purity of 99% is required.

Schulze's Maceration Mixture. A mixture of potassium chlorate 1 (moistened with water), with nitric acid 40; or a solution of 0.06 g. potassium chlorate in water 100 ml. and 1 ml. of nitric acid. For separation of muscle fibre in animal, and ligneous tissue in vegetable, histology. Distinguish from the following:—

Schulze's Chlor-Zinc-Iodine Reagent for Cellulose. Dissolve 110 g. of zinc in 300 ml. of pure hydrochloric acid, and evaporate to 150 ml. (sp. gr. about 1.8). Dissolve separately 12 g. of potassium iodide in as little water as possible; add 0.15 g. of iodine. Mix the solutions, and filter if necessary through asbestos.—Bower and Gwynne Vaughan.

Potassii Hydroxidum (*B.P.* '32). $\text{KOH} = 56.10$. Contains total alkali, by titration with N/1 sulphuric acid to methyl orange, equivalent to not less than 85% of KOH . Potassii Hydroxidum, *U.S.P. X*, contains not less than 85% of KOH . Assayed to exclude carbonate by precipitation with barium chloride, adjustment to volume with air-free water, filtration and titration of a portion with N/1 hydrochloric acid to phenolphthalein.

Liquor Potassii Hydroxidi (*B.P.* '32). Contains from 4.75% to 5.25% w/v of total alkali, calculated as KOH . Liquor Potassii Hydroxidi, *U.S.P. X*, contains from 4.5% to 5.5% w/v of KOH , assayed by the barium chloride precipitation method.

Sodii Hydroxidum (*B.P.* '32). $\text{NaOH} = 40.00$. Contains not less than 95% of total alkali, calculated as NaOH . The *U.S.P. X* substance, assayed similarly to the potassium compound, contains not less than 90% of NaOH .

Sodii Bicarbonas (*B.P.* '32). $\text{NaHCO}_3 = 84.00$. Contains from 99% to the equivalent of 101% of NaHCO_3 . The *U.S.P. X* substance, after drying over sulphuric acid, contains not less than 99% of NaHCO_3 .

The B.P. Limit Test for Carbonate. The test for carbonate in sodium bicarbonate is not sensitive to less than about 4%, but the assay would condemn a sample, if dry, containing 2% of sodium carbonate.—W. H. Linnell, *Pharm. J.*, ii/1932, 531.

The pH of 1% sodium bicarbonate solution is raised from 8.37 to 8.60 by the addition of 2.05% of normal carbonate. In practice, owing to the limited

accuracy of the official method, a considerably higher percentage would escape notice. The following is a more sensitive test:—1 g. NaHCO_3 is dissolved in CO_2 -free water, exactly 10 ml. of 0.01% phenolphthalein solution is added, and the solution diluted to 100 ml. in a Nessler glass. A comparison solution is prepared by diluting 5 to 10 ml. N/10 NaOH and exactly 0.3 ml. of the same phenolphthalein solution to 100 ml. in a second Nessler glass. The test solution must not be deeper than the comparison solution.—C. Morton, *Pharm. J.*, 1933, 3.

Sodii Carbonas (B.P. '32). $\text{Na}_2\text{CO}_3 \cdot 10\text{H}_2\text{O} = 286.15$. Contains from 99% to the equivalent of 102% of the pure substance.

Sodii Carbonas Exsiccatus (B.P. '32). $\text{Na}_2\text{CO}_3 = 106.0$. Loses not more than 2% at 110° , and then contains not less than 99.5% of Na_2CO_3 .

Sodii Carbonas Monohydratus (U.S.P. X). Rendered anhydrous by gentle ignition, contains not less than 99.5% of Na_2CO_3 . Loss at 110° , 10% to 15%.

Sodii Chloras (B.P.C. '34). $\text{NaClO}_3 = 106.5$. Contains not less than 99% of NaClO_3 .

Sodii Fluoridum (B.P.C. '34). $\text{NaF} = 42.00$. Contains not less than 90% of NaF . Assayed by titration at 80° of a solution in carbonate-free alkali, in the presence of sufficient neutral sodium chloride to saturate at end of titration, with M/10 potassium aluminium sulphate, using methyl red as indicator.

Sodium Fluosilicate is useful as an insecticide, being both a contact and stomachic poison. It has the advantages over arsenicals of cheapness, more rapidly killing, being non-poisonous to humans, and of effectiveness against a wide range of insects. Mixed with 9 parts of hydrated lime, it has been successfully used as a field dust against many pests.—*Chem. & Drugg.*, i/1925, 452.

For insects and lower organisms, e.g. worms and protozoa, sodium fluosilicate is more toxic than sodium arsenite. To man and the higher animals the arsenicals are 9 times more toxic than sodium fluosilicate and 30 times more toxic than sodium fluoride.—S. Marcovitch, *J. Pharmacol.*, Oct. 1928, 185.

Lithii Carbonas (B.P.C. '34). $\text{Li}_2\text{CO}_3 = 73.88$. Assayed by titration with excess acid and sodium hydroxide, a purity of not less than 98.5% on the dried substance should be indicated. Loss at 100° , not more than 1%. Lithii Carbonas, N.F. V., after drying to constant weight at 100° , contains not less than 98.5% of Li_2CO_3 ; leaves not more than 0.15% of residue insoluble in dilute acetic acid.

(For other salts of potassium and sodium see under the respective acids.)

PYRETHRI FLOS

Pyrethri Flos (B.P.C. '34). Contains not less than 0.4% of pyrethrin I. Ash limit, 8%. Acid-insoluble ash limit, 1%. Assayed by the B.P.C. '34 process: continuously extract 10 g. (in 85 powder) with petroleum (b.p. 40° to 50°); reflux the solution (measuring about 50 ml.) with 5 ml. of N/1 sodium hydroxide in methyl alcohol, in a micro-Kjeldahl apparatus, on a water-bath for 2 hours; acidify the cooled mixture with N/1 sulphuric acid and steam distil till 150 ml. of aqueous distillate is collected below the light petroleum; extract the whole distillate in a separator with the addition of 10 g. of sodium chloride, with the light petroleum and two further portions; the petroleum liquids and alcohol and water rinsings of the separator are titrated with N/50 sodium hydroxide till a distinct pink colour is produced to phenolphthalein after vigorous shaking; deduct the blank titration required for the light petroleum, 1 ml. of N/50 sodium hydroxide is equivalent to 0.0066 g. of pyrethrin I.

Flos Pyrethri, *P. Helv. V*, yields to ether by continuous extraction not less than 5% of extractive; ash, not more than 8.5%.

Freshly-ground pyrethrum flowers, in containers of different kinds, lose from 30% to 43·6% of pyrethrins within a year. Powdered and ground flowers in closed tins continue to lose pyrethrins for more than 2 years but not so rapidly. Storage under suitable conditions is therefore important.—C. B. Grading and C. S. Corl, *Ind. Engng Chem.*, 1932, 901.

Fly Sprays. An efficient fly spray should contain not less than 0·09 of total pyrethrin. Killing-power is increased by the use of a wetting-agent such as coconut oil soap or diglycololeate.—*Pharm. J.*, i/1933, 129.

PYROXYLINUM

Pyroxylinum (*B.P.* '32). The substance dried at 100° for one hour contains 11·5% to 12·3% of nitrogen. Viscosity at 20° of a 3% *w/v* solution of the dry substance in acetone, not less than three poises. To determine the nitrogen content, a weighed portion of the dried substance is transferred with nitrogen-free sulphuric acid to a mercury-filled nitrometer and shaken, and the liberated nitric oxide measured. Pyroxilinum, *U.S.P. X*, saturated with alcohol in a dish placed in cold water, ignited at the top and afterwards heated to redness, leaves not more than 0·3% of ash. Yields not more than 0·3% of water-soluble substances.

RHEUM

Rheum (*B.P.* '32). Rhubarb should contain not more than 2% of foreign organic matter. Ash, not more than 15%. Alcohol (45%) soluble extractive, not less than 35%. Rheum, *U.S.P. X*, yields not less than 30% of diluted alcohol-soluble extractive and complies with a test for rhapontic rhubarb.

Rhizoma Rhei, *P. Helv. V*, yields not more than 13% of total ash and not more than 1% of acid-insoluble ash; it contains from 4·23% to 6·56% of free and combined anthracene derivatives calculated as chrysophanic acid, and complies with the following test for the absence of rhapontic rhubarb:—Boil 10 g. of powdered rhubarb with 50 ml. of dilute alcohol for 15 minutes; filter and evaporate the filtrate to 10 ml.; allow to cool and treat with 15 ml. of ether; after 24 hours no crystals should be deposited which when dried and treated with concentrated sulphuric acid produce a purple-red colour.

Fluorescence Test for Rhapontic Rhubarb. On exposure to ultra-violet light rhapontic rhubarb exhibits a violet fluorescence, while genuine Chinese rhubarbs give a velvety brown fluorescence.

Using genuine Chinese rhubarb as a standard for comparison, one can easily detect as little as 1% of added rhapontic rhubarb, using paper strips soaked in a tincture made from the drug. The whole operation must be conducted in a dark room. The wide variation in the intensities of the fluorescence of different samples of rhapontic rhubarb makes it very difficult to carry out exact quantitative determinations by this method.—T. E. Wallis and E. R. Withell, *Quart. J. Pharm.*, 1934, 574.

Evaluation on chrysophanic acid content, the results not being absolute, but well adapted for comparative purposes.—A. Tschirch and P. Schmitz, *Quart. J. Pharm.*, 1929, 463.

Physiological experiments on mice with rhubarb extracts made *in vacuo* showed same to be more effective.—*Pharm. J.*, i/1924, 6.

Pulvis Rhei Compositus. Methods of analysis.—J. F. Liversedge and co-workers, *Yearb. Pharm.*, 1926, 456.

In the *B.P.* formulæ for pills, vegetable drugs such as aloes, ginger, etc., are taken in "fine powder," and it may be assumed therefore that Pulv. Asafoet. is not sanctioned in Pil. Aloes et Asafoet., or Pulv. Myrrh. in Pil. Rhei Co. Since both these powders are well known in commerce it would have been helpful if the monographs on these and other vegetable drugs had provided the user with information as to which drugs were official in powder form.—*Pharm. J.*, ii/1932, 147.

SACCHARINUM

Saccharinum (*B.P.C.* '34). $C_7H_5O_3NS = 183.1$. Determined by the *B.P.* method for Saccharinum Solubile, it contains not less than 97% of the pure substance. M.p., not below 225° . Glusidum, *U.S.P. X*, leaves not more than 0.5% of ash, and complies with tests for glucose and lactose, benzoic or salicylic acid and ammonium compounds.

Saccharinum Solubile (*B.P.* '32). $C_7H_4O_3NSNa, 2H_2O = 241.1$. Contains not less than 98% of the pure substance. M.p. of the washed and dried separated saccharin, not lower than 226° . Complies with tests for absence of benzoate and salicylate and limit of *p*-sulphaminobenzoic acid. Assayed by the *B.P.* '32 process: boil 0.7 g. with 10 ml. of 30% sodium hydroxide solution for 2 minutes; cool and reflux with 15 ml. of hydrochloric acid for 50 minutes; cool, rinse condenser with 50 ml. of water, and remove acid vapours with a current of air; distil the ammonia liberated on addition of 20 ml. of 30% sodium hydroxide solution into excess N/10 sulphuric acid and back titrate with N/10 sodium hydroxide to methyl red. Glusidum Solubile, *U.S.P. X*, complies with tests for neutrality, benzoate or salicylate, ammonium compounds, etc.

SANTONICA

Santonica (*B.P.C.* '34). Contains not less than 2% of santonin. Assayed by maceration with chloroform, filtration, recovering most of the chloroform from a portion of the filtrate, and with addition of 1.2% baryta, heating off the remaining chloroform; extraction of the filtered and washed acidified liquid is effected with chloroform; the residue after evaporation of the solvent is dissolved in dehydrated alcohol, diluted with hot water to 15% w/w of alcohol and filtered; after 24 hours the separated santonin is collected on a tared filter, washed with 15% w/w alcohol and dried; a correction for loss due to solubility is allowed.

Flores Cinæ, *P.G. VI*, by the process prescribed, yields not less than 2% of santonin. Flos Cinæ, *P. Helv. V*, is required to show a santonin content of not less than 1.8%.

Santoninum (*B.P.* '32). $C_{15}H_{18}O_3 = 246.1$. M.p., 171° to 174° . Ash, not more than 0.1%. 0.1 g. with 2 ml. of sulphuric acid is not darker than pale brown, and on dissolving forms a clear solution not darker than yellow. The alcoholic solution should be neutral to litmus. Santoninum, *U.S.P. X*, leaves not more than 0.1% of ash. 0.5 g. boiled with 20 ml. of water and 2 ml. of dilute sulphuric acid, cooled and filtered, produces no cloudiness with Mayer's reagent or with iodine solution, even after standing for 3 hours.

A tentative quantitative method for the determination of santonin in mixtures and tablets is described in Methods of Analysis (*A.O.A.C.*, 1930, 472).

SAPONES

Sapo Animalis (*B.P.* '32). Curd soap loses at 110° , 20% to 30%. In powder, loss at 110° , not more than 5%. Solidifying point of the fatty acids, not less than 42° . Limit tests for alkali hydroxide, and free fatty acids, alkali carbonate and free fat are described.

For *toilet purposes* special soap bases are employed containing a large proportion of stearates (tallow). A proportion of palm oil is generally combined with the tallow. The soap is ultimately converted by machinery into ribbon-shaped shreds; it is perfumed and after other treatment is stamped in moulds. Free alkali is rarely present in appreciable amount.

For *shaving soap* it is necessary to employ fats—"strong" tallow—with a high melting-point.

Pure potassium palmitate makes an excellent shaving soap, improved with a little glycerin. Sodium palmitate and sodium stearate are not suited—they are not sufficiently soluble.—H. L. Smith, *Pharm. J.*, ii/1915, 33.

Shaving paste with pearly lustre can be made with beef tallow and potassium hydroxide, replacing $1/6$ th of the KOH with sodium hydroxide.—*ibid.*

Sapo Durus (*B.P.* '32). Hard soap loses at 110° , 20% to 30%. In powder, loss at 110° , not more than 5%. Constants of the free fatty acids: solidifying-point, 18° to 23° ; $n_{D40^{\circ}}$, 1.454 to 1.458; acid value, 195 to 205; iodine value, 83 to 92. Complies with tests for absence of cottonseed oil, sesame oil and arachis oil. Limit tests for alkali hydroxide and free fatty acid, alkali carbonate, free fat, and chloride and other alcohol-insoluble substances are included. Sapo, *U.S.P. X*, dissolved in alcohol, evaporated with sand, and dried at 110° , loses not more than 36%, or 10% for powdered soap; iodine value of the fatty acids, 84 to 90.

The *B.P.* figure of 0.5% for free fat in soaps is too low. The limit for Sapo Durus should be raised to 1%, for Sapo Mollis to 0.7%, and for Sapo Animalis to 0.7% to 0.8%.—Report of Sub-Committee, *Analyst*, 1934, 104.

Castile Soap (Jabón Castilla). By a Spanish Royal Order (Dec. 14, 1927) the name must apply only to a soap prepared in Spain, in the manufacture of which no fats other than olive oil have been used: containing not more than 2% chlorides (as sodium chloride): maximum water content 25%: maximum free alkali content 0.3%. The soap must be white and must be soluble in water or alcohol without residue.—*Pharm. J.*, i/1928, 164.

Mottle is produced by adding iron or residues and scrapings of the lye tanks.

Household Soaps are made with vegetable oils of light gravity.

Good average soap can be produced by saponifying vegetable oils, such as cottonseed, palm, or coconut (of this the best variety is known as "White Cochin" oil, the second as "Ceylon" oil); but these oils, containing much of the oleic ester, produce more soluble, i.e., wasteful soaps.

The use of **resin** in household soap is not injurious. It renders the soap smooth, prevents efflorescence, and cleansing "odour" imparted is appreciated. Yellow bar soaps contain some 10% to 25%. Its chief *raison d'être* is probably cheapness. It is not, however, suitable for toilet purposes, and a large admixture cannot be allowed. Occasional additions to common soaps are chlorophyll, sodium silicate and French chalk. **Sodium Silicate** has latterly come into use. Remarkable data are given by Smith. (*loc. cit.*)

Transparent Soaps are made by setting from methylated spirit. Many contain resin and sugar (as much as 20% of each). Only about half the spirit is recovered—the rest is lost in drying. In Germany manufacturers may use pure spirit with 1 kilo of castor oil and 400 ml. of soda solution per 100 litres of spirit to "denature" it.

A method of determining the detergent action of soaps depends on the quantity of carbon which the soap solution will carry through filter paper. The "**carbon number**" is the number of grammes carried by 1 kg. of solution under standard conditions.—J. W. McBain and co-workers, *J. Soc. chem. Ind.*, Lond., 1923, 273.

Marine Soaps are made from coconut oil and palm nut oil. These oils contain, combined as glycerin esters, mainly lauric and myristic acids, with

me palmitic and oleic. They also contain caproic, caprylic, and capric acids. The presence of the three last-mentioned is of importance because they render a soap made with coconut oil not easily salted out by sea water.—H. L. Smith, *Pharm. J.*, ii/1915, 33.

Sapo Kalinus (*B.P.C.* '34). Potash soap yields, by the *B.P.* method for Sapo Mollis, not less than 44% of fatty acids of linseed oil, having an iodine value of 179 to 210. Complies with limit tests for chlorides and other alcohol-insoluble substances, alkali hydroxide, alkali carbonate, and free fatty acid. Sapo Mollis, *U.S.P. X*, made from linseed oil, loses not more than 52% at 110°. Alcohol-insoluble matter, not more than 3%. Free KOH, 0.1% to 0.25%. Sapo kalinus, *P.G. VI*, contains not less than 40% of the fatty acids of linseed oil.

Sapo Mollis (*B.P.* '32). Soft soap yields not less than 44% of fatty acids or olive oil having the characters given under Sapo Durus. Complies with limit tests for chloride and other alcohol-insoluble substances, alkali hydroxide, alkali carbonate, free fatty acid, and free fat. Assayed by extraction of the acidified solution with light petroleum (b.p., 50° to 60°), drying at 80°.

Soft Soaps for Insecticides. The specification of the Association of British Insecticide Manufacturers (Bulletin No. 82: Ministry of Agriculture and Fisheries) requires soft soap for spraying purposes to dissolve completely in distilled water to a clear solution, to contain not more than 1% of free caustic alkali (KOH) or 3% of free alkali carbonate (K_2CO_3); not less than 95% of total alkali, expressed as K_2O , to be K_2O . Percentage of fatty and resin acids to be declared.

It will be of interest to know if there will ever be any hard or soft soap which is truly *B.P.* These soaps are made from olive oil, but the lower grade oil is not permitted to be used except for official liniments, ointments and plasters, so that soaps may only be made from olive oil with an acid value not exceeding 2. In so far as soft soap is used in *Lin. Saponis* it may be said that it may be prepared from the lower grade oil. However, in parts of the Empire where olive oil is not readily obtainable, arachis oil or sesame oil may be employed in place of olive oil in making official liniments, plasters, ointments and soaps.—*Chem. & Drugg.*, ii/1932, 622.

SCILLA

Scilla (*B.P.* '32). Ash, not more than 6%. No biological assay is included and no standard is recommended by the Permanent Commission on Biological Standardisation of the League of Nations, since the biological assay of squill estimates the cardiac glycosides present, which are not the constituents responsible for its expectorant effect for which it is chiefly used in medicine.

The *U.S.P. X* states that "Tincture of Squill injected into the ventral lymph sac of a frog has a minimum systolic dose of not less than 0.0055 cc. and not more than 0.0065 cc.; equivalent to not less than 0.00000046 Gm. and not more than 0.00000054 Gm. of ouabain for each Gm. of body weight of frog." Thus ouabain is prescribed as standard for squill and 100 ml. of a tincture of squill should be equivalent to 8.3 mg. of ouabain. Ouabain is, however, an unsuitable standard for squill if different methods of assay are to be permitted, since the relative potency of squill and ouabain differs according to the species (see Burn, *Pharm. J.*, i/1927, 328).

Red Squill. Red squill has a similar content of cardiac glycosides to white squill, as shown by Wokes and Willimott (*Quart. J. Pharm.*, 1934, 565). It has in addition constituents which are toxic for rats, and is therefore used as a rat poison. These are not wholly absent from white squill. Wokes and Willimott (*loc. cit.*) found that when they prepared a dried powder from the two varieties, the dose of the red squill necessary to kill half the rats was 1.0 to 1.5 g. per kg.,

whereas the dose of the white squill was ten times as great. These doses were given by mouth.

Scillaren is a crystalline glycoside of squill which could be used as a standard for biological estimations of squill if it were not a proprietary preparation. The average potency of tincture of squill, *B.P.* '32, is equivalent to that of a 0.013% solution of scillaren.

SENNA

Sennæ Folium (*B.P.* '32). Contains not more than 1% of stalks and not more than 2% of other foreign organic matter. Ash limit, 12%. Acid-insoluble ash limit, 3%. Senna, *U.S.P. X* contains not more than 10% of stems and not more than 2% of pods or other foreign organic matter. Acid-insoluble ash, not more than 3%. Folium Sennæ, *P. Helv. V*, consists only of the leaflets of *Cassia angustifolia* (Tinnevelly senna), and may give up to 12% of ash.

Senna Constituents. An examination of Tinnevelly leaves, leaves grown at Lima (botanically identical), and Alexandrian leaves, yielded salicylic acid, rhein ($C_{18}H_8O_6$), kempferol, aloe-emodin and other bodies. The purgative action is in part due to the aloe-emodin—and other bodies.—F. Tutin, *Pharm. J.*, ii/1913, 741; *Chem. & Drugg.*, ii/1913, 43.

Senna and gum arabic. Account of French Government Expedition by Perrot and Alland in the Sudan with a view to acquiring knowledge for cultivation in the French African Colonies.—H. G. Greenish, *Pharm. J.*, ii/1920, 488.

Sennæ Fructus (*B.P.* '32). Contains not more than 2% of foreign organic matter. Fructus Sennæ, *P. Helv. V*, is the dry fruit of *Cassia acutifolia* and of *Cassia angustifolia*, and should yield not more than 6% of ash.

The standard is expressed in a very exceptional manner, and allows the presence of 2% of any other pods or even of dirt. Many of these new standards for crude drugs appear to be based on the *U.S.P. X*, but are unsatisfactory because they do not discriminate between harmless admixture and dangerous foreign organic matter. The *B.P.* dose, which is expressed in grains, does not assist those who wish to prescribe a definite number of pods, and might have been given as 4 to 12 pods.—*Pharm. J.*, ii/1932, 186.

Ether shaken with a slightly acidified senna extract gives the Bornträger reaction—a pink or red colour with ammonia water. If the ether be shaken with a saturated solution of nickel acetate, the aqueous layer turns red, and if this be separated and potassium hydroxide added a violet precipitate forms, which is stated to be a characteristic test for senna.—*U.S.D.*, 1926.

SINAPIS

Black Mustard contains the glycoside sinigrin, i.e., potassium myronate, $C_{10}H_{16}KNS_2O_9$, with myrosin, which is similar to the ferment emulsin in bitter almonds. This glycoside splits up under the influence of water with evolution of allyl isothiocyanate— $C_3H_5NCS=99.112$, the principal constituent of the essential oil, potassium acid sulphate and glucose. *P.G. VI* requires black mustard seeds to yield at least 0.7% of the allyl compound.

White Mustard Seeds (*Sinapis alba*) do not yield allyl mustard oil, but *p*-oxybenzyl isothiocyanate, *syn. acrinyl isothiocyanate*, $C_6H_4OH \cdot CH_2O \cdot NCS$. The **sinalbin** contained in the seeds under the influence of myrosin and water decomposes forming that oil, sinapin acid sulphate, and glucose. The oil in question has a sharp taste. It decomposes on heating. It is insoluble in water but readily in alcohol or ether. As the black seeds contain an excess of their glycoside and the white an excess of the ferment, the combination of the two

duces the strongest effect. Some work by Prof. Greenish, however (*Pharm. J.*, i/1912, 203), shows that in all the samples of black mustard seed examined—both old and new—there was sufficient myrosin to decompose all the sinigrin present, and that properly preserved black mustard seeds retain their myrosin impaired for many years. Two samples examined contained sufficient myrosin to decompose a much larger quantity of sinigrin than the seeds themselves contained.

J. Gadamer has made a close study of these various constituents—see Schmidt, *Pharm. Chem.*, Vol. II., Sections 1 and 2, for the latest views.

The practice of adding farina (wheat starch) to mustard producing the mixed article "**Condiment**" Mustard is legalised by the 1875 Food and Drugs Act. The best table mustard contains about 12% to 14%.—*Pharm. J.*, i/1917, 470.

With one or two exceptions most manufacturers now retain the fixed oil in "Condiment" Mustard.—*cf.* Vol. I., p. 756.

The Food and Drug Administration of the U.S. Dept. of Agriculture define mustard seed as the seed of *Sinapis alba* L. (white mustard), *Brassica nigra* L. (black mustard), *B. juncea* (L.) Cosson, or varieties or related species of the two latter. *Sinapis alba* contains no appreciable amount of volatile oil: contains not more than 5% of total ash and not more than 1.5% of ash insoluble in hydrochloric acid. *Brassica nigra* and *B. juncea* yield 0.6% of volatile mustard oil: varieties and species of these two yield not less than 0.6% of volatile mustard oil of similar character and composition. These mustard seeds yield not more than 5% of total ash, nor more than 1.5% of ash insoluble in hydrochloric acid.

GROUND MUSTARD SEED, mustard meal: unbolted ground mustard seed, conforming to standards for mustard seed. **MUSTARD CAKE** is ground mustard seed minus a portion of the fixed oil. **MUSTARD FLOUR**, ground mustard, "mustard": the powder made from mustard seed with the hulls largely removed and with or without removal of portion of fixed oil: contains not more than 5% of starch, nor more than 6% of total ash. **PREPARED MUSTARD**: a paste composed of a mixture of ground mustard seed and/or mustard flour and/or mustard cake, with salt, vinegar, with or without sugar and/or dextrose, spices or other condiments. In the fat-, salt-, and sugar-free solids, it contains not more than 24% of carbohydrates, not more than 12% of crude fibre, nor more than 5.6% of nitrogen.—*S.R.A.*, *F.D. No. 2*, *Rev. 4*, Aug. 1933.

Oleum Sinapis Volatile (*B.P.C.* '34). Contains not less than 92% *w/w* of C_3H_5NCS . Sp. gr., 1.014 to 1.025; n_{D20° , 1.525 to 1.530. Assayed by heating in alcoholic dilution under a reflux condenser on a water-bath for 30 minutes with N/10 silver nitrate and strong solution of ammonia, followed by adjustment to volume, filtration and titration of an aliquot part with N/10 ammonium thiocyanate. **Oleum Sinapis Volatile**, *U.S.P. X*, yields not less than 93% *w/v* of C_3H_5NCS . Sp. gr. at 25°, 1.013 to 1.020; n_{D20° , 1.5268 to 1.5280.

Essential oil of black mustard (b.p., 150.7°) is suitable for preserving wines, being 200 times as efficient as sulphurous acid, and not affecting colour, odour or taste of the wine. 1 ml. of 1% solution per litre is usually sufficient.—*Perfum. essent. Oil Rec.*, 1924, 84.

Determination of essential oil of mustard in black mustard.—Miesemaeker and Boivin, *J. pharm. Chim.*, Paris, 1930, 122, 478, per *Perfum. essent. Oil Rec.*, 387.

Odour and constitution of mustard oil, with table of specifications for mustard oil in eight pharmacopœias.—Dyson, *Perfum. essent. Oil Rec.*, 1929, 42.

STRAMONIUM

Stramonium (*B.P.* '32). Contains not more than 2% of foreign organic matter, not more than 20% of stems, not more than 1% of stems greater than 4 mm. in width, and not less than 0.25% of alkaloids of stramonium, calculated as hyoscyamine. Ash limit, 20%. Acid-insoluble ash limit, 4%. Assayed by the *B.P.* process for *Belladonnæ Folium*.

Stramonium, *U.S.P. X*, yields not less than 0.25% of alkaloids, not more than 4% of acid-insoluble ash and contains not more

than 3% of stems over 8 mm. in diameter. Assayed by percolation with ether-chloroform mixture, transferring to sulphuric acid extraction with chloroform and titration of the alkaloid as described for *Belladonnæ Folia*, *U.S.P. X*. *Folium Stramonii*, *P. Helv. V*, contains not less than 0.2% of alkaloid and may yield up to 21% of ash.

STROPHANTHINUM

Strophanthinum (*B.P. '32*). Adjusted by admixture with lactose to possess an activity equal to 40% of that of anhydrous ouabain. Loss on drying in a vacuum desiccator over sulphuric acid, not more than 3%. Ash, not more than 1%.

Wokes (*Quart. J. Pharm.*, 1928, 513) examined a series of commercial samples testing them in comparison with ouabain, and found them to vary from 25% to 60% of the potency of ouabain.

Distinction between Strophanthin and Ouabain. Strophanthin is soluble in water 1 in 40 to 43 at 15°. The aqueous solution of this glycoside, unlike that of ouabain, gives a persistent froth on agitation.

The following distinguishing colour test has been proposed: 5 ml. of concentrated hydrochloric acid, a few crystals of resorcinol and a trace of the glycoside are warmed to 60° or 70°. Ouabain gives no colouration, while strophanthin gives a rose colour.—*J. chem. Soc. Abstr.*, ii/1921, 601.

Hispidus strophanthin, like *kombé* strophanthin, is a mixture of two glycosides.—*Brit. chem. Abstr.*, Dec., 1928, 1376.

B.P. '32 Assay. Samples are compared with a standard preparation of strophanthin the potency of which has been accurately determined in relation to anhydrous ouabain. The method used for assay is one of those described under *Digitalis Pulverata*. There is no standard for strophanthin in the *U.S.P. X*.

Strophanthin-G (Ouabain). This is the official strophanthin of the German Pharmacopœia. It is referred to in the *B.P. '32* and the *U.S.P. X* only as standard for biological assays. It is not an official preparation in these Pharmacopœias because supplies for therapeutic use are believed to be insufficient. It is a crystalline substance of constant composition except that it may contain different amounts of water of crystallisation. The international standard ouabain contains 20% of water of crystallisation. On crystallisation at the ordinary temperature $C_{30}H_{46}O_{12} \cdot 9H_2O$ is obtained, whereas if the temperature is 30° or 60° the crystals contain four and three molecules of water respectively.

Spinal rather than anæsthetised cats should be used for the assay of cardiac glycosides. In the assay of strophanthin by the cat method, the grouping of the figures is improved if a non-volatile anæsthetic be used instead of ether and still further improved by using spinal animals. The interval between the preparation of the cat and the infusion should be about 4 hours.—A. D. Macdonald, *Quart. J. Pharm.*, 1934, 182.

Strophanthus (*B.P. '32*). From *Strophanthus kombé*. Foreign organic matter, not more than 2%. Ash, not more than 5%. Semen *Strophanthi*, *P.G. VI*, consists of the seeds of *Strophanthus gratus* (Wallich and Hooker) Franchet, and contains not less than 4% of anhydrous g-strophanthin. Semen *Strophanthi*, *P. Helv. V*, is the seed of *Strophanthus kombé* Oliver.

The geographical range of *S. kombé* is limited. It might be well to order the use of *S. hispidus* instead—it is more easily obtained and is the only other species giving the green colour with sulphuric acid.—E. M. Holmes, *Pharm. J.*, i/1913, 33.

Recent specimens of *S. kombé* are much mixed with *S. Courmontii*, while samples of *S. hispidus* can no longer be found unadulterated in commerce, and are entirely, or in large proportion, seeds of *S. sarmentosus*. A useful table gives the characters of *Strophanthus* species found in commercial samples.—F. J. Mathieson, per *Quart. J. Pharm.*, 1928, 260, 262.

100% *kombé* seeds were available in 1929, but their price was 50% higher than that for the mixed variety.

Four colour tests are recommended for the identification of the seeds of various species of *Strophanthus*.—E. M. Smelt, *Quart. J. Pharm.*, 1933, 467.

Tinctura Strophanthi (*B.P.* '32). Tincture of strophanthus is compared with a standard tincture of strophanthus by one of the biological methods prescribed under *Digitalis Pulverata*, and is diluted to be of the same potency as the standard tincture. This standard is equivalent to a 0.42% solution of the international standard ouabain (crystalline strophanthin-g), or to a 0.33% solution of anhydrous ouabain as determined by a biological comparison made by the frog method.

Seeds of *Strophanthus Emini*. The results now accumulated indicate that the seeds of this species of strophanthus are similar in their pharmacological action to those of *S. kombé*, that the tincture made from them presents no difficulties in biological assay, and that the mixture of glycosidal principles obtained from them is similar in chemical composition and in therapeutic effects to the strophanthin obtained from the seeds of *S. kombé*.—British Pharmacopœia Commission, *Quart. J. Pharm.*, 1935, 61.

Preparation of Strophanthin-E. The crushed seeds of *S. Emini* were freed from fat by light petroleum and extracted by percolation with alcohol (90%) at laboratory temperature. The percolate was concentrated under reduced pressure and treated with a slight excess of basic lead acetate. After filtration the solution was freed from lead by excess of hydrogen sulphide. The solution was saturated with ammonium sulphate, and the sticky precipitate which formed was extracted with alcohol. The alcoholic solution was either neutralised with a little sodium hydroxide and precipitated with ether or precipitated without neutralisation. The strophanthin was dried at 100° *in vacuo*. The yield is from 5% to 7% of the fat-free seeds, and is similar to that obtained from *S. kombé*.—I. D. Lamb and S. Smith, *Quart. J. Pharm.*, 1935, 1.

Tincture of strophanthus, *U.S.P. X*, is required to be equivalent to a 0.83% solution of ouabain (*U.S.P.* ouabain contains less water of crystallisation than international standard ouabain) as determined by the one-hour frog method. This is a short statement of the actual requirement which reads "Tincture of strophanthus injected into the ventral lymph sac of a frog has a minimum systolic dose of not less than 0.00,005,5 cc. and not more than 0.00,006,5 cc., equivalent to not less than 0.00,000,046 Gm., and not more than 0.00,000,054 Gm. of ouabain for each Gm. body weight of frog." Thus the *U.S.P.* tincture appears to be about twice as strong as the *B.P.* tincture, but this is not so. Tinctures tested in comparison with ouabain by the one-hour method appear to be much stronger than when tested by the 24-hour method of *B.P.* '32, because the rate of absorption of the *kombé* glycosides present in the tincture is greater than that of the ouabain.

Chemical Assay. Haycock's Method. The powdered seeds (20 g.) are freed from oil with petroleum ether and exhausted with alcohol 70%. This tincture is evaporated at a low temperature, dissolved in 100 ml. of water, filtered, 3.2 ml. of sulphuric acid (25%) added, then shaken out thrice with 10 ml. of ether. The aqueous acid solution is warmed for 1 hour at not exceeding 5°. This decomposes the strophanthin present into strophanthidin and strophanthobiose methyl ether. It is then cooled and shaken out with 10 ml. of chloroform. This is evaporated to a low bulk, allowed to crystallise out and dried below 65°. The result divided by the factor 0.365 gives the amount of strophanthin present. Various samples of the seed by this method gave 3.1% to 3.57% strophanthin. A standard of 0.1% *w/v* strophanthin is suggested.—J. Haycock, *Pharm. J.*, i/1911, 553.

FROMME'S 1910 ASSAY METHOD. Consists in first extracting with absolute alcohol under a reflux, evaporating and defatting the extract. This is boiled with water and a few drops of lead acetate solution and then filtered, using kieselguhr. The glycoside is next decomposed by heating with hydrochloric acid, and finally the strophanthidin is thoroughly extracted with chloroform and weighed. This multiplied by 2.187 gives the weight of strophanthin represented. A similar process is used for the tincture.—W. Kroseberg, *Pharm. J.*, i/1914, 590.

Tinctura Strophanti, *P. Helv. V*, contains from 0.19% to 0.21% of strophanthin determined by conversion to strophanthidin and multiplying by the factor 0.158.

SULPHUR

Sulphur Præcipitatum (*B.P.* '32). $S=32\cdot06$. Residue on ignition, not more than 0·5%. Consists, when examined microscopically, of grouped amorphous globules without crystalline particles. The *U.S.P.* *X* substance, dried over sulphuric acid, contains not less than 99·5% of *S*. Assayed by oxidation of solution in potassium hydroxide with hydrogen peroxide, and precipitation as barium sulphate. Residue on ignition, not more than 0·5%.

Sulphur Sublimatum (*B.P.* '32). Residue on ignition, not more than 0·25%. Consists, when examined microscopically, chiefly of almost opaque rounded, amorphous particles or aggregates, occasionally associated with semi-crystalline masses. The *U.S.P.* *X* substance, dried to constant weight over sulphuric acid and assayed by precipitation as barium sulphate, contains not less than 99·5% of *S*. Residue on ignition, not more than 0·5%.

Assay of Preparations. The sample to be assayed, containing 0·1 g. of *S* is weighed accurately into a 175 ml. conical flask and 50 ml. of a solution containing 40 g. of potassium cyanide A.R., 90 ml. of triethanolamine and water to 1000 ml., is added together with 1 g. of soft paraffin. A little pumice is added to prevent superheating, and the mixture is vigorously boiled for $\frac{1}{2}$ hour under a reflux condenser. The liquid is cooled, treated with 10 ml. formaldehyde solution and acidified with dilute nitric acid, and 50 ml. of *N/10* silver nitrate is added. The mixture is decolorised if necessary with charcoal, filtered, the residue washed, and the filtrate titrated with *N/10* ammonium thiocyanate using ferric alum as indicator. A blank is carried through on 10 ml. of the reagent. Each ml. of *N/10* AgNO_3 is equivalent to 0·003206 g. of *S*.—*N. L. Allport, Quart. J. Pharm.*, 1933, 431.

Sulphur in flowers of sulphur, sulphur ointment, confection of sulphur, sulphur tablets and compound liquorice powder may be determined by boiling the material (equivalent to about 0·1 g. of sulphur) in a conical flask attached to a reflux condenser with 2 g. of crystalline sodium sulphite and 30 to 40 ml. of water until all the sulphur has dissolved. The addition of 1 g. of soft paraffin assists solution. Cool, pour off from the paraffin and wash the residue with water, add 10 ml. of solution of formaldehyde and 10 ml. of 20% acetic acid to remove the excess of sulphite, and titrate the thiosulphate formed in the solution with *N/10* iodine, using starch as indicator; 1 ml. of *N/10* iodine is equivalent to 3·206 mg. of sulphur.—*H. R. Fleck and A. M. Ward, Quart. J. Pharm.* 1934, 179.

Sulphuris Iodidum (*B.P.C.* '34). Contains not less than 70% of *I*. Assayed by titration of a triturate with potassium iodide solution, with *N/10* sodium thiosulphate. 0·5 g. of Sulphuris Iodidum, *N.F. V*, requires not less than 28 ml. of *N/10* sodium thiosulphate.

Baryta Sulphurata (*B.P.C.* '34). Contains not less than 60% of BaS . Assayed by titration with ammoniacal zinc solution, using alkaline lead indicator externally.

Calx Sulphurata (*B.P.C.* '34). Contains not less than 50% of CaS . Assayed by the *B.P.C.* process—1 g. mixed with 10 ml. of water, 25 ml. of copper sulphate solution, and 10 ml. of dilute hydrochloric acid is warmed on a water bath for 15 minutes, cooled and diluted to 100 ml. 25 ml. of the filtered mixture (the first 25 ml. is rejected) with 1 g. of potassium iodide is titrated with *N/10* sodium thiosulphate, using starch mucilage as indicator; a blank experiment is performed.

Calcium sulfuratum solutum, *P. Helv. V* (Soluté de Vlemingx), contains 6% *w/v* of polysulphide sulphur. **Assay:** Boil for 2 minutes in a 100 ml. wide-mouthed flask 60 ml. of water with 1 g. of boric acid and a few pieces of porous pot. Add rapidly and cautiously 0·2 g. of potassium cyanide and the 1 ml. of the sulphur solution, and boil for 10 minutes. After cooling, transfer to a 100 ml. graduated flask, and add sufficient water to make 100 ml. Take 50 ml. of this solution, acidify with 1 or 2 ml. of concentrated hydrochloric acid and add bromine water until a yellow colour persists in the solution. Remove the excess of bromine by adding phenol solution and allow to stand for 15 minutes; add 1 g. of potassium iodide, and after 15 minutes titrate the liberated

ine with N/10 sodium thiosulphate, using starch as indicator towards the end of the titration. Each ml. of N/10 thiosulphate is equivalent to 0.001603 g. of polysulphide sulphur.

Lime-Sulphur Solution. The specification of the Association of British Pesticide Manufacturers (Bulletin No. 82: Ministry of Agriculture and Fisheries) for lime-sulphur solution requires it to be clear and free from sludge and of sp. gr. about 1.3, with not less than 18.5% *w/w* of polysulphide sulphur equivalent to about 24% *w/v*.

Potassa Sulphurata (B.P. '32). Contains 42% to 45% of total sulphur. Assayed by precipitation of a solution in sodium hydroxide solution oxidised with bromine solution, with barium chloride. Potassa Sulphurata, U.S.P. X, contains not less than 12.8% of S in combination as sulphide; assayed by addition of a copper sulphate solution to a solution of the substance, filtering and adding of a hydrogen sulphide solution to the filtrate, acidified with acetic acid; no black precipitate should be produced.

THYMOL

Thymol (B.P. '32). $C_{10}H_{14}O = 150.1$. M.p., 48° to 51°. Residue on evaporation from an open dish on a water-bath, not more than 0.05%. The solution in alcohol is neutral to litmus and optically inactive. Oily drops do not separate on standing from a 10% *w/v* solution in 10% *w/v* sodium hydroxide solution, which is clear and colourless or pale red.

Thymolis Iodidum (B.P.C. '34). $C_{20}H_{24}O_2I_2 = 550.0$. By the B.P. method described under Iodophthaleinum, the substance dried over sulphuric acid contains not less than 40% of I. Loss over sulphuric acid, not more than 5%. Unphosphated ash, not more than 3%. Thymolis Iodidum, U.S.P. X, contains, after drying over sulphuric acid, not less than 43% of iodine. Assayed by fuming with potassium carbonate, oxidising the solution with potassium permanganate, decolorising with alcohol, filtering, adding potassium iodide to a portion, acidifying and titrating with sodium thiosulphate.

Oleum Thymi (B.P.C. '34). By the B.P. method for eugenol in Oleum Caryophylli, it contains not less than 40% *w/v* of phenols. Sp. gr., 0.905 to 0.960; n_{D20} , 1.483 to 1.510. Soluble in 2 volumes of alcohol (80%). Oleum Thymi, N.F. V., contains not less than 20% *v/v* of phenols. Sp. gr. at 25°, 0.894 to 0.930. Assayed by measurement of the volume of oil unabsorbed by sodium hydroxide solution.

Thyme. The Food and Drug Administration of the U.S. Dept. of Agriculture define thyme as the dried leaves and flowering tops of *Thymus vulgaris* L.: contains not more than 14% of total ash, nor more than 4% of ash insoluble in hydrochloric acid.—S.R.A., F.D., No. 2, Rev. 4, Aug. 1933.

Oleum Ajowan (B.P.C. '34). By the B.P. method for eugenol in Oleum Caryophylli, the unabsorbed oil measures not more than 6 ml., equivalent to not less than 40% *v/v* of thymol. Sp. gr., 0.910 to 0.930; α_D , 0° to +2°; n_{D20} , 1.485 to 1.510.

Sage. The Food and Drug Administration of the U.S. Dept. of Agriculture define sage as the dried leaf of *Salvia officinalis* L.: contains not more than 2% of stems (excluding petioles) and other foreign matter.—S.R.A., F.D., No. 2, Rev. 4, Aug. 1933.

THYROIDEUM

Thyroideum (B.P. '32). Contains 0.09% to 0.11% of iodine in combination as thyroxine, and not more inorganic iodine than 0.0% of the total iodine. Assayed for total iodine by fusion of a solution obtained by boiling for 4 hours with N/1 sodium hydroxide and filtering, with sodium hydroxide and potassium nitrate; addition of sodium metabisulphite solution and sufficient

phosphoric acid to render faintly pink to methyl orange, oxidation with bromine and, with the addition of sodium salicylate, potassium iodide and phosphoric acid, titration with N/200 sodium thiosulphate. Inorganic iodine is determined by the same method on a cold water extract. Thyroideum, *U.S.P. X*, contains 0.17% to 0.23% of iodine in thyroid combination, and is free from iodine in inorganic or any other form of combination than that peculiar to thyroid gland.

Glandulæ Thyreoideæ siccatae, *P.G. VI*, is standardised to contain not less than 0.18% of iodine. Thyreoidea siccata, *A. Helv. V*, is prepared by drying the chopped glands below 50° and adjusting the defatted powder, if necessary, with lactose to contain from 0.08% to 0.1% of thyroxine. The product should contain not more than 2% of fat, 8.5% of moisture, and yield not more than 5% of ash.

Iodine can be found in thyroid both as thyroxine and also as di-iodotyrosine; the latter is inactive, and it appears more logical to standardise in terms of thyroxine only. Various evidence suggests that the matter is not so simple as this. Gaddum and Hetherington (*Quart. J. Pharm.*, 1931, 183) found that some samples of thyroid were active in proportion to the thyroxine present but that others were not. They determined the activity by observing the effect on the oxygen consumption of small animals. At the present time opinion is changing to the view that the total iodine is a better guide to activity than thyroxine iodine.

Assay. The use of a cold water extract of desiccated thyroid for the determination of the inorganic iodine as advocated in the *B.P. '32* is inapplicable in the case of preparations which have been desiccated at low temperatures, since a considerable proportion of the thyroglobulin will not be denatured and will be extracted by the water.—H. G. Rees and A. H. Salway, *Quart. J. Pharm.* 1932, 627.

A preparation obtained by low-temperature desiccation is most readily brought into line with the *B.P.* assay process by leaving in contact with alcohol for 17 hours and drying at 55° to 60°.—C. R. Harington and S. S. Randal, *ibid.*, 629.

Total iodine and acid-insoluble iodine determinations in thyroid gland are described. The standardisation of thyroid on a basis of acid-insoluble iodine content requires only one determination of iodine. It is unnecessary to fix a standard for total iodine content, and determinations of "inorganic" iodine no longer serve any useful purpose.—G. Middleton, *Analyst*, 1932, 603.

Inorganic iodides in dry thyroid may be determined by shaking 0.2 to 3 g. for 2½ hours in a stoppered tube with 20 ml. of cold methyl alcohol, filtering and washing with methyl alcohol; the extract is evaporated and the iodine in the residue determined.—W. Lawson, *Biochem. J.*, 1933, 112.

The faults found with **Hunter's method**, as modified in the *U.S.P.*, are a loss of iodine on acidifying the solution of carbonates with phosphoric acid and the introduction of oxychlorine compounds, including chloric acid, by the use of sodium hypochlorite solution. These compounds also liberate iodine from potassium iodide, and are not eliminated by boiling. With due care during neutralisation the first-mentioned source of error can be minimised, and when a fair proportion of iodine is present, error due to oxychlorine compounds is negligible.

The removal of chlorine by boiling after acidification should be controlled by starch-iodide paper until no reaction is obtained and the solution then boiled for a further 15 minutes, instead of boiling for 30 minutes as directed. When the iodine content is considerably less than 0.2%, a modification of Kendall's method is best. One gramme of the substance is gently heated with powder of caustic soda in a nickel crucible over an Argand burner. The crucible is heated more strongly until all the organic matter is oxidised, but no nitrate is added. The melt is extracted with water and filtered. Using bromophenol blue as indicator, the mixture is neutralised with phosphoric acid (sp. gr., 1.75). Excess

mine water is added, and an excess of 2 ml. of phosphoric acid. The liquid is boiled to half its volume to expel bromine, the remaining traces being eliminated by adding salicylic acid after cooling. The iodine is liberated from the iodate by the addition of potassium iodide solution and the iodine titrated with N/200 sodium sulphate.—Wilfred Smith, *Quart. J. Pharm.*, 1928, 372.

Variations in Iodine Content. The iodine content of thyroid glands varies in different countries and at different seasons. W. H. Martindale found in Japan, in one instance, a content of 0.514% in the dry gland (equivalent to 0.1% iodine in the fresh gland). On another occasion in March he found from the same source 0.24% iodine in dry gland (equivalent to 0.063% in the fresh gland; 1 part of dry thyroid = 3.82 of fresh gland). The weight of the lobes of these glands varied enormously—from 15 to 90 grains. Further, he obtained thyroids from a number of English South Down sheep slaughtered in January—these glands may be considered as a typical winter collection. The fresh substance yielded 25% Thyroideum Siccum (i.e., 1=4 of fresh gland). On the same day he found the dry gland to contain 0.368% iodine, equivalent to 0.092% iodine in the fresh gland.

In June, 1929, sheep's thyroids imported from the Argentine and closely examined, yielded 27% dried gland with an iodine content of 0.378%. The iodine content in the fresh gland was evidently 0.102%.

According to an American authority:—

Sheep's thyroids	may contain up to 0.04% in the fresh gland.	
Pigs'	0.0084 to 0.288%	ditto
Ox	0.003 to 0.147%	ditto
Human	0.006 to 0.08%	ditto

N. H. Martin, *Pharm. J.*, ii/1912, 144, found as average in the dry gland from July to November, 1911, 0.36%, and in fresh gland 0.091%, and from December, 1911, to May, 1919, in dry 0.33%, and in fresh 0.086%. It is, however, more instructive to compare the content in the months of April to October inclusive with the November to March figures on the fresh gland. The former are about double the latter owing to greater moisture content in the winter. The iodine yield from dry gland works out about the same throughout the year, viz., 0.34%.

Martin, in continuing his investigations, arrived at 0.25% as a fair iodine standard on examination of 13,927 lobes.—*Pharm. J.*, ii/1913, 123.

The variation in the total iodine and thyroxine iodine contents of fresh gland and dried defatted glands is so great that there can be no satisfactory correlation between thyroid B.P. '32 and preparations expressed in terms of fresh gland or unstandardised dried defatted gland.

The relative activities of thyroid, U.S.P. X, and thyroid, B.P. '32, are approximately $74 \pm 12 : 100$.—R. F. Corran, J. Pritchard and F. E. Rymill, *Quart. J. Pharm.*, 1935, No. 3.

Biological Methods of Assay. There are three biological methods for estimating the activity of thyroid. An early method was that introduced by Reid Hunt, known as the acetonitrile test, which depends on the rise in resistance to acetonitrile produced in mice by the administration of thyroid. A dose of acetonitrile injected into each of a group of mice will kill a certain percentage. If the mice have previously received thyroid the same dose will kill a smaller percentage. Two samples of thyroid can thus be compared by observing what reduction in the percentage each causes. The relative potency of the two samples is, of course, not directly proportional to the respective reductions in percentage mortality, but can be determined from previous experiments in which the effect of different doses of the same sample of thyroid has been determined.

A second method of observing the physiological action of thyroid is to determine its effect on oxygen consumption, or on carbon dioxide production. The oxygen consumption of guinea-pigs, rabbits or rats can be estimated by placing the animal in a metal chamber immersed in water at constant temperature. The chamber contains a soda-lime tower to absorb carbon dioxide, and oxygen is admitted as required through a bubble trap. The passage of each bubble of oxygen is recorded on a smoked paper by a mechanical device, and the number of bubbles in a given period of time is a measure of the oxygen consumption. The volume of a bubble is previously determined when calibrating the instrument. The administration of thyroid raises the oxygen consumption, and different samples of thyroid can be compared by finding what doses produce the same rise in oxygen consumption.

A third method of estimating the potency of thyroid is by means of its effect in causing loss of body weight in guinea-pigs. Two groups of six guinea-pigs may be taken and their weights observed from day to day. One sample of thyroid is administered to one group, daily for six days, while a second sample, to be compared with the first, is administered to the second group. The mean loss of weight in each group can then be determined. The more potent sample produces the greater loss in weight; the relative potency of two samples is more rapidly found by finding a dose of one which produces an effect lying between the effects produced by two doses of the other.

Thyroxine sodium (*B.P.* '32). $C_{15}H_{10}O_4NI_4Na = 798.8$. Contains from 61 to 65% of I. Assayed by the ignition method described under Thyroideum, using a solution in 2N sodium hydroxide and adding albumen. Thyroxinum, *U.S.P.* contains not less than 63% of iodine; it is assayed by igniting the substance dried over sulphuric acid for 24 hours, with potassium carbonate, treating the water extractive with potassium permanganate, discharging the colour with alcohol, filtering, and titrating a portion of the filtrate, after adding potassium iodide and acid, with N/200 sodium thiosulphate.

The relation of the activity of the thyroid to the iodine compounds occurring in the gland is not clear. The seasonal variation in the total iodine of samples of thyroid material from different parts of the U.S.A. was considerable—January and February 100 lb. of thyroid contained 14 g. of iodine and in July and August as much as 40 g. This variation was not observed in material from England and Scotland. In the summer, when the iodine content is highest, the percentage of total iodine in the form of **thyroxine** is not more than 10%, and in the winter less than 5%—i.e. from 90% to 95% of the total iodine is in some form other than thyroxine. Chemical change can occur in thyroxine not only when the glands are desiccated, but when they are allowed to stand after being freshly ground. The thyroxine is chemically altered and cannot be isolated, but it is still physiologically active. There appears to be another iodine compound present in the gland, which is destroyed with alkali, partly stable to acid, and has the physiological activity of thyroxine. Thyroxine may be an intermediate form of the active constituent and it must be altered before it can become physiologically active—the alteration possibly being the attachment of a second hydroxyl group to the thyroxine.—*Lancet*, ii/1928, 176.

Parathyroid Extract.

Biological Method of Assay. The potency of parathyroid extract has been determined by injecting it subcutaneously into dogs to observe whether a rise in the amount of serum calcium occurs. This method suffers from the disadvantage that a given dose produces a different effect in different dogs, and the maximum rise occurs at a variable time. A more accurate method has been proposed by Dyer, who found that the injection of the extract into rats causes a rise in the amount of urinary calcium. Dyer (*Quart. J. Pharm.*, 1933, 426) uses ten rats which are placed in separate cages to allow collection of the urine. The output of calcium is determined, the urine of five rats being pooled, and the urine of the other five also being pooled. These observations are made for two or three days. The one group of rats is then injected with the extract which is used as standard, and the second group with the preparation which is being tested. The injections are given daily for two or three days. If the potency of the doses given is exactly equal, the rise in output of calcium in the two groups is the same.

If the potency of the doses is not exactly equal, the dose with the greater potency produces the greater rise in urinary calcium. But it is not possible to calculate the relative potency of doses which produce unequal rises in calcium output. When unequal rises occur, the experiment must be repeated until a dose of the unknown preparation is found which produces the same rise as a dose of the standard.

TRAGACANTHA

Tragacantha (*B.P.* '32). Foreign organic matter, not more than 2%. The powder does not acquire a pink colour in ruthenium red solution. Ash limit, 4%. Tragacantha, *U.S.P.* X, complies with tests for foreign gums and Indian gum.

The following test provides a means of comparing specimens of tragacanth, but it is necessary that tests should be carried out at the same time and under exactly the same conditions if comparative results are to be obtained:—The tragacanth should be in the form of powder, or, if in flake form, should be reduced to a powder which passes a No. 30 sieve and is retained by a No. 60 sieve. Prepare a mucilage of 1.25% strength as described in the *B.P.* for Mucilago Tragacanthæ; heat for 1 hour on a boiling water-bath, with occasional stirring, pour it into a 50 ml. Nessler cylinder and allow it to stand overnight. At the surface of this mucilage release a steel ball, $\frac{5}{32}$ in. in diameter, and take the time of fall from a point 1.5 in. to a point 4 in. below the upper surface; the time required is from 50 to 150 seconds for average specimens of tragacanth when freshly powdered. Occasional specimens give much higher results.

The comparison between samples of gum tragacanth should be made by comparison of the viscosities of 0.4% aqueous mucilages in poises at 20.0°. If a gum gives a mucilage with a viscosity above 1.3 poises it may be regarded as of good quality.—L. A. Haddock, *Quart. J. Pharm.*, 1934, 505.

Its most important character is its power to form a mucilage, yet no test, such as the falling ball method, is included in the *B.P.* for distinguishing different qualities.—*Pharm. J.*, ii/1932, 208.

A tentative quantitative method for the determination of "Volatile Acidity" of Tragacanth is described in Methods of Analysis (*A.O.A.C.*, 1930, 475).

VALERIANA

Valeriana (*B.P.* '32). Foreign organic matter, not more than 5%. Ash, not more than 10%. The *U.S.P. X* requires a foreign matter limit of 5% and an acid-insoluble ash limit of 10%.

Ferri Valerianas (*B.P.C.* '34). Residue on ignition, not less than 24%.

Sodii Valerianas (*B.P.C.* '34). $C_5H_9O_2Na = 124.1$. Contains not less than 85% of the pure substance. Assayed by titration of a solution with N/2 sulphuric acid to bromophenol blue removing most of the acid produced with ether.

Zinci Valerianas (*B.P.C.* '34). $C_{10}H_{18}O_4Zn, 2H_2O = 303.6$. On treatment with nitric acid and gentle ignition, yields 25% to 28% of ZnO.

ZINCUM

Zinci Carbonas (*B.P.C.* '34). Residue on ignition, not less than 68%.

Zinci Oxidum (*B.P.* '32). $ZnO = 81.38$. Loses not more than 1% on ignition, and then contains not less than 99% of ZnO. Assayed by dissolving the substance and ammonium chloride in excess N/1 sulphuric acid and back titrating with N/1 sodium hydroxide to methyl orange. The *U.S.P. X* omits the ammonium chloride in the titration, and requires a purity of 99% in the freshly ignited substance.

Zinci Oleostearas (*B.P.C.* '34). By the *B.P.* method for Zinci Stearas, it contains 12% to 14% of zinc, calculated as ZnO.

Zinci Stearas (*B.P.* '32). Contains zinc equivalent to from 13% to 15.5% of ZnO. Assayed by boiling in excess of N/10 sulphuric acid for 10 minutes, filtering and titrating the filtrate and washings with N/10 sodium hydroxide to methyl orange.

Emplastrum Zinci Oxidi (*B.P.C.* '34). Weight per sq. yd., not less than 8 oz., and of the base cloth 4 oz., and the difference between these weights not less than 4 oz. The cotton cloth complies with the standard for the cotton cloth of Emplastrum Adhesivum.

Calamina (*B.P.C.* '34). Residue on ignition, 68% to 90%. Matter insoluble in hydrochloric acid, not more than 1%.

Titanic Chloride, $TiCl_4$, is kept in sealed tubes. It reacts violently with water and forms a white precipitate. On adding ammonia complete precipitation of the hydroxide occurs.

Liquid titanium chloride hydrolyses quickly in moist air with a dense white smoke, and is used for smoke-screens, sky-writing, etc.—F. P. Stroup. *Amer. J. Pharm.*, Aug., 1928, 504.

Titanous Chloride, TiCl_3 , is supplied in 15% solution which is used as a reducing agent and employed in volumetric analysis for the determination of iron and of organic nitro-compounds. N/10 solution is prepared by diluting approximately 1 volume with 1 volume of concentrated hydrochloric acid and 8 volumes of water and standardising immediately before use with N/10 ferric ammonium sulphate. It should be freshly prepared, or preserved in an atmosphere of hydrogen or carbon dioxide.

Titanic Oxide, TiO_2 . A white powder, extremely insoluble in ordinary solvents. It does not dissolve in boiling nitric acid or aqua regia. Used as an ingredient of toilet powders and as a white pigment in place of "White Lead." RUTILE is the ore titanium dioxide used in leather dyeing.

Titanous Sulphate, $\text{Ti}_2(\text{SO}_4)_3$, usually supplied in 15% solution, is employed as a reducing agent.

ZINGIBER

Zingiber (B.P. '32). Alcohol (90%)-soluble extractive, not less than 4.5%. Water-soluble extractive, not less than 10%. Ash limit, 6%. Water-soluble ash, not less than 1.7%. Zingiber, U.S.P. X, yields not less than 2% of non-volatile ether-soluble extractive and not less than 12% of cold water extractive.

The Food and Drug Administration of the U.S. Dept. of Agriculture define ginger as the washed and dried, or decorticated and dried, rhizome of *Zingiber officinale* Roscoe. Contains not less than 42% of starch, not more than 8% of crude fibre, not more than 1% of lime, not less than 12% of cold-water extract, not more than 2% of ash insoluble in hydrochloric acid, nor less than 2% of ash insoluble in cold water. *Jamaica Ginger*: Ginger grown in Jamaica, containing not less than 15% of cold-water extract and otherwise as ginger. *Limed Ginger*, bleached ginger: whole ginger coated with calcium carbonate: contains not more than 4% of calcium carbonate nor more than 10% of total ash, and otherwise as ginger.—S.R.A., F.D. No. 2, Rev. 4, Aug. 1933.

The reaction between acids and the common metals is a matter frequently arising and one concerning which information is not always available. In arranging the following table it was necessary to check many of the interactions experimentally, as we found statements in the literature to vary greatly.

SUBSTANCE	HYDROCHLORIC ACID Conc.* Sp. gr. 1.16	Dilute* Sp. gr. 1.048	SULPHURIC ACID Conc.* Sp. gr. 1.84	Dilute* Sp. gr. 1.069	NITRIC ACID Conc.* Sp. gr. 1.42	Dilute† Sp. gr. 1.057	REMARKS
Aluminium	Hot. Soluble. Forms AlCl_3 .	Easily soluble. Forms AlCl_3 .	Soluble. Forms $\text{Al}_2(\text{SO}_4)_3$.	Slowly attacked.	Soluble. Forms $\text{Al}(\text{NO}_3)_3$ and oxides of nitrogen. Scarcely attacked.	Soluble. Forms oxides of nitrogen. Slowly attacked.	Attacked by NaOH or KOH solutions. Soluble in cold acetic acid, more quickly in hot.
	Cold. Ditto.	Ditto.	Slightly attacked.	Unattacked.	Slowly soluble. Forms $\text{Al}(\text{NO}_3)_3$. Ditto.	Slowly soluble. Forms $\text{Al}(\text{NO}_3)_3$. Ditto.	<i>Ignited</i> (amorphous) oxide is unattacked by acids, except hot H_2SO_4 .
	Hot. Slightly soluble. Forms AlCl_3 .	Slowly soluble. Forms AlCl_3 . Ditto.	Slightly soluble. Ditto.	Soluble. Forms $\text{Al}_2(\text{SO}_4)_3$. Ditto.	Slowly soluble. Forms $\text{Al}(\text{NO}_3)_3$. Ditto.	Slowly soluble. Forms $\text{Al}(\text{NO}_3)_3$. Ditto.	
	Cold. Almost insoluble.	Ditto.	Ditto.	Ditto.	Ditto.	Ditto.	
Antimony	Hot. Pure antimony is insoluble.	Slightly soluble.	Soluble. Forms $\text{Sb}_2(\text{SO}_4)_3$ and SO_2 .	Insoluble.	Oxidised but not dissolved.	No action.	Aqua Regia dissolves, forming antimonious or antimonie chloride according to duration of action.
	Cold. No action.	No action.	No action.	Insoluble.	Practically no action.	No action.	
	Hot. Forms SbCl_5 .	Slightly soluble.	Soluble.	Slightly soluble.	Practically insoluble.	Very slightly soluble.	Soluble in KOH and NaOH solutions. Insoluble in NH_4OH .
	Cold. Slowly soluble to form SbCl_3 .	No action.	Slightly soluble.	No action.	Ditto.	No action.	

* = B.P. '32.

† = B.P.C.

SUBSTANCE	HYDROCHLORIC ACID Conc.* Sp. gr. 1.16	SULPHURIC ACID Conc.* Sp. gr. 1.84	NITRIC ACID Conc.* Sp. gr. 1.42	REMARKS
Antimonious Oxide, Sb_2O_3	Hot. Soluble. Forms $SbCl_3$.	Soluble. Forms $SbOCl$ more or less according to proportion of acid.	Slightly sol- uble.	Soluble in acetic, tartaric and benzoic acids, also in glycerin.
	Cold. Slowly sol- uble.	Slightly sol- uble.	Slightly sol- uble.	
Arsenic	Hot. Slowly sol- uble. Forms $AsCl_3$. Cold. Practically no action	Soluble. Forms As_2O_3 and SO_2 . No action.	Soluble. Forms H_3AsO_4 . No action.	Easily soluble in Aqua Regia forming $SbCl_3$ or $SbCl_5$, according to duration of action.
	Hot. Soluble. Forms $AsCl_3$ and chlor- ine on pro- longed boil- ing.	Soluble.	Soluble.	
Arsenic Oxide, As_2O_3 .	Cold. Soluble with- out change.	Ditto.	Ditto.	Soluble in sodium hypo- chlorite solution.
	Hot. Soluble. Forms $AsCl_3$.	Soluble.	Soluble.	
Arsenous Oxide, As_2O_3 .	Hot. Soluble. Forms $AsCl_3$.	Slightly sol- uble.	Soluble. Forms H_3AsO_4 .	Soluble in alkalis.
	Cold. Ditto.	Slowly sol- uble.	Ditto.	

SUBSTANCE	HYDROCHLORIC ACID		SULPHURIC ACID		NITRIC ACID		REMARKS
	Conc.* Sp. gr. 1.16	Dilute* Sp. gr. 1.048	Conc.* Sp. gr. 1.84	Dilute* Sp. gr. 1.069	Conc.* Sp. gr. 1.42	Dilute† Sp. gr. 1.057	
Bismuth	Hot. Scarcely acted on.	No action.	A slightly soluble basic sulphate formed and SO ₂ .	No action.	Soluble. Forms Bi(NO ₃) ₃ and oxides of nitrogen.	Soluble. Forms Bi(NO ₃) ₃ or BiONO ₃ according to quantity of acid.	Aqua Regia converts into BiCl ₃ .
	Cold. Insoluble.	Ditto.	Scarcely acted on. Schmidt says forms Bi ₂ (SO ₄) ₃ .	Ditto.	Ditto.	Scarcely acted on.	
Bismuth Oxide Bi ₂ O ₃ .	Hot. Soluble. Forms BiCl ₃ .	Soluble.	Slightly soluble. Forms Bi ₂ (SO ₄) ₃ . Very slightly soluble.	Slightly soluble. Forms Bi ₂ (SO ₄) ₃ . Very slightly soluble.	Soluble. Forms Bi(NO ₃) ₃ .	Soluble. Forms Bi(NO ₃) ₃ .	Soluble in strong hot NaOH solution.
	Cold. Ditto.	Ditto.			Ditto.	Ditto.	
Chromium (Reduced from CrCl ₃ by Zn.)	Hot. Soluble. Forms CrCl ₃ , quickly oxidising to CrCl ₃ .	Soluble.	Easily soluble.	Easily soluble. Forms CrSO ₄ , quickly oxidising to Cr ₂ (SO ₄) ₃ . Scarcely acted on.	Practically no action.	Insoluble.	Assumes the "passive" condition in contact with nitric acid and other oxidising agents.
	Cold. Ditto.	Very slightly soluble.	Insoluble.		Insoluble.	Insoluble.	
	Hot. Soluble. Forms CrCl ₃ . Cold. Ditto.	Soluble. Forms CrCl ₃ . Ditto.	Soluble. Forms Cr ₂ (SO ₄) ₃ . Ditto.	Soluble. Forms Cr ₂ (SO ₄) ₃ . Ditto.	Soluble. Forms Cr(NO ₃) ₃ (?) Cr(NO ₃) ₃ (?). Ditto.	Soluble. Forms Cr(NO ₃) ₃ . Ditto.	Crystalline Cr ₂ O ₃ is insoluble in all acids.

† Note.—By dissolving strongly heated chromic oxide in hot concentrated HNO₃ (Sp. gr. 1.4) a solution is obtained from which Cr₂(NO₃)₆, 15H₂O crystallises on cooling. In dry air this loses 6H₂O with formation of Cr₂(NO₃)₆, 9H₂O.

SUBSTANCE	HYDROCHLORIC ACID		SULPHURIC ACID		NITRIC ACID		REMARKS
	Conc.* Sp. gr. 1·16	Dilute* Sp. gr. 1·048	Conc.* Sp. gr. 1·84	Dilute* Sp. gr. 1·069	Conc.* Sp. gr. 1·42	Dilute† Sp. gr. 1·057	
Chromic Oxide, CrO_3 (Red).	Hot. Soluble. Forms CrCl_3 and chlorine.	Soluble without decomposition less the solution be very concentrated Soluble without decomposition.	Soluble. Forms $\text{Cr}_2(\text{SO}_4)_3$ and oxygen.	Soluble without decomposition.	Soluble without decomposition.	Soluble without decomposition.	Very soluble in water to form H_2CrO_4 .
	Cold. Ditto.		Soluble without decomposition.	Ditto.	Ditto.	Ditto.	
Cobalt	Hot. Soluble. Forms CoCl_2 .	Soluble. Forms CoCl_2 .	Attacked. Forms CoSO_4 and SO_2 .	Soluble. Forms CoSO_4	Soluble. Forms $\text{Co}(\text{NO}_3)_2$ and oxides of nitrogen. Ditto.	Soluble. Forms $\text{Co}(\text{NO}_3)_2$ and oxides of nitrogen. Ditto.	
	Cold. Ditto.	Ditto.	Unattacked.	Ditto.	Soluble. Forms $\text{Co}(\text{NO}_3)_2$. Ditto.	Soluble. Forms $\text{Co}(\text{NO}_3)_2$. No action.	
Cobalt (ous) Oxide.	Hot. Soluble. Forms CoCl_2 .	Soluble. Forms CoCl_2 .	Soluble. Forms $\text{Co}(\text{SO}_4)$. Ditto.	Not attacked.	Soluble. Forms $\text{Cu}(\text{NO}_3)_2$ and oxides of nitrogen.	Soluble. Forms $\text{Cu}(\text{NO}_3)_2$ and oxides of nitrogen.	Slowly soluble in concentrated solutions of caustic alkalis.
	Cold. Ditto.	Ditto.		Ditto.	Ditto.	Ditto.	
Copper	Hot. Very slowly soluble. Forms Cu_2Cl_2 (in contact with the air).	Very slightly soluble.	Slowly soluble. Forms CuSO_4 , CuS and SO_2 .	Not attacked.	Ditto.	Scarcely attacked.	
	Cold. Not attacked.	Not attacked.	Not attacked.	Not attacked.			

SUBSTANCE	SULPHURIC ACID		NITRIC ACID		REMARKS
	Conc.* Sp. gr. 1.16	Dilute* Sp. gr. 1.048	Conc.* Sp. gr. 1.84	Dilute* Sp. gr. 1.069	
Copper (-ic) Oxide, (Black), CuO.	Hot. Soluble. Forms CuCl ₂ .	Soluble. Forms CuCl ₂ . Ditto.	Soluble. Forms CuSO ₄ . Slightly sol- uble.	Soluble. Forms CuSO ₄ . Ditto.	Slowly soluble in hot concentrated solutions of caustic alkalis. Ditto.
	Cold. Ditto.				
Copper (ous) Oxide, (Red) Cu ₂ O.	Hot. Soluble. Forms Cu ₂ Cl ₂ .	Forms Cu ₂ Cl ₂ .	Soluble. Forms CuSO ₄ and copper.	Soluble. Forms CuSO ₄ and copper.	Ditto.
Gold (ic) Oxide, Au ₂ O ₃ .	Cold. Forms CuCl ₂ and Copper.	Forms CuCl ₂ and Copper.	Forms CuSO ₄ and SO ₂ .	Ditto.	Ditto.
Gold	Hot Not attacked.	Not attacked.	Not attacked.	Not attacked.	Soluble in Aqua Regia to form AuCl ₃ . Soluble in conc. KOH solution and KCN solution.
	Cold. Ditto.	Ditto	Ditto.	Ditto.	
Iron	Hot. Slightly soluble.	Slightly soluble.	Slightly soluble.	Slightly soluble.	Soluble in conc. KOH solution and KCN solution.
	Cold. Ditto.	Ditto.	Ditto.	Ditto.	
Iron	Hot. Soluble. Forms FeCl ₂ .	Soluble. Forms FeCl ₂ .	Soluble. Forms FeSO ₄ and SO ₂ .	Soluble. Forms FeSO ₄ .	Soluble. Forms Fe(NO ₃) ₃ and oxides of nitrogen. Ditto.
	Cold. Ditto.	Ditto.	No action.	Ditto.	
Iron	Hot. Soluble. Forms Fe(NO ₃) ₃ and oxides of nitrogen.	Soluble. Forms Fe(NO ₃) ₃ and oxides of nitrogen.	Soluble. Forms Fe(NO ₃) ₃ and oxides of nitrogen.	Soluble. Forms Fe(NO ₃) ₃ and oxides of nitrogen.	Soluble. Forms Fe(NO ₃) ₃ and oxides of nitrogen. Ditto.
	Cold. Ditto.	Ditto.	Rendered passive.	Ditto.	

SUBSTANCE	HYDROCHLORIC ACID Conc.* Dilute* Sp. gr. 1.16 Sp. gr. 1.048		SULPHURIC ACID Conc.* Dilute* Sp. gr. 1.84 Sp. gr. 1.069		NITRIC ACID Conc.* Dilute† Sp. gr. 1.42 Sp. gr. 1.057		REMARKS
Iron (-ic) Oxide, Fe_2O_3 .	Hot. Soluble. Forms Fe_2Cl_6 .	Soluble. Forms Fe_2Cl_6 .	Forms $\text{Fe}_2(\text{SO}_4)_3$ which dis- solves on dilution. Action slight.	Very slight action.	Very slight action.	Practically no action.	Strongly ignited oxide practically insoluble in all acids.
	Cold. Action slight.	Practically no action.	Action slight.	Practically no action.	Practically no action.	Ditto.	
Lead	Hot. Action slight. Forms PbCl_2 .	Action very slight.	Action very vigorous. Forms PbSO_4 .	Action very slight.	Action slow. Forms $\text{Pb}(\text{NO}_3)_2$ and oxides of nitrogen.	Action vigorous. Forms $\text{Pb}(\text{NO}_3)_2$ and oxides of nitrogen.	Action greatly depends on the condition of the lead—whether sheet or finely divided, etc.
	Cold. Action very slight.	Ditto.	Action very slight.	Ditto.	Action slight.	Action slight.	
Lead Oxide (Litharge), PbO .	Hot. Soluble. Forms PbCl_2 .	Soluble. Forms PbCl_2 .	Forms PbSO_4 .	Forms PbSO_4 .	Readily sol- uble. Forms $\text{Pb}(\text{NO}_3)_2$.	Easily sol- uble. Forms $\text{Pb}(\text{NO}_3)_2$.	Soluble in conc. KOH and NaOH solutions, easily in acetic acid.
	Cold. Ditto.	Ditto.	Ditto.	Ditto.	Ditto.	Ditto.	
Magnesium	Hot. Easily sol- uble. Forms MgCl_2 .	Easily sol- uble. Forms MgCl_2 .	Soluble. Forms MgSO_4 , $\text{Mg}(\text{HSO}_4)_2$ and SO_2 .	Soluble. Forms MgSO_4 .	Soluble. Forms $\text{Mg}(\text{NO}_3)_2$, oxides of nitrogen, hydrogen and ammon. nitrate.	Soluble. Forms $\text{Mg}(\text{NO}_3)_2$, hydrogen and oxides of nitrogen.	Soluble in ammonium chloride solution.
	Cold. Ditto.	Ditto.	Action very slight.	Ditto.	Ditto.	Ditto.	

SUBSTANCE	HYDROCHLORIC ACID		SULPHURIC ACID		NITRIC ACID		REMARKS
	Conc.* Sp. gr. 1.16	Dilute* Sp. gr. 1.048	Conc.* Sp. gr. 1.84	Dilute* Sp. gr. 1.069	Conc.* Sp. gr. 1.42	Dilute† Sp. gr. 1.057	
Magnesium Oxide, MgO.	Hot. Readily sol- uble. Forms MgCl ₂ .	Readily sol- uble. Forms MgCl ₂ .	Readily sol- uble. Forms MgSO ₄ and Mg(HSO ₄) ₂ .	Readily sol- uble. Forms MgSO ₄	Readily sol- uble. Forms Mg(NO ₃) ₂ .	Readily sol- uble. Forms Mg(NO ₃) ₂ .	Soluble in ammonium salts, also in organic acids.
	Cold. Ditto.	Ditto.	Ditto.	Ditto.	Ditto.	Ditto.	
Manganese	Hot. Easily sol- uble. Forms MnCl ₂ .	Easily sol- uble. Forms MnCl ₂ .	Soluble. Forms MnSO ₄ and SO ₂ .	Easily sol- uble. Forms MnSO ₄ .	Easily sol- uble. Forms Mn(NO ₃) ₂ and oxides of nitrogen. Ditto.	Easily sol- uble. Forms Mn(NO ₃) ₂ and oxides of nitrogen. Ditto.	
	Cold. Ditto.	Ditto.	Action slight.	Ditto.			
Manganese Dioxide, MnO ₂ .	Hot. Soluble. Forms MnCl ₂ and chlorine.	Soluble. Forms MnCl ₂ and chlorine.	Action slight. Forms MnSO ₄ and oxygen at 200° [or Mn ₂ (SO ₄) ₃ at 100°]— Schmidt.	Action very slight. Forms MnSO ₄ and oxygen.	Action very slight.	Action very slight.	MnO ₂ is more soluble in diluted sulphuric acid in presence of easily oxidisable bodies (FeSO ₄ , sugar, etc.), with formation of MnSO ₄ and O, the O then oxidises the sub- stances in question.
	Cold. Ditto.	Action slight.	Practically no action.	No action.	No action.	No action.	

SUBSTANCE	HYDROCHLORIC ACID Conc.* Sp. gr. 1·16	Dilute* Sp. gr. 1·048	SULPHURIC ACID Conc.* Sp. gr. 1·84	Dilute* Sp. gr. 1·069	NITRIC ACID Conc.* Sp. gr. 1·42	Dilute† Sp. gr. 1·057	REMARKS
Mercury	Hot. No action.	No action.	Forms HgSO_4 , SO_2 , no action. and Hg_2SO_4 according to proportions and temperature. No action.	Practically	Soluble. Forms $\text{Hg}(\text{NO}_3)_2$ and oxides of nitrogen.	Soluble. Forms $\text{Hg}(\text{NO}_3)_2$ and oxides of nitrogen.	
	Cold. Ditto.	Ditto.		Ditto.	Soluble. Forms $\text{Hg}(\text{NO}_3)_2$ and some $\text{Hg}_2(\text{NO}_3)_2$ and oxides of nitrogen.	Very slightly soluble. Forms $\text{Hg}_2(\text{NO}_3)_2$.	
Mercury (-ic) Oxide, (Yellow or red variety), HgO.	Hot Soluble. Forms HgCl_2 .	Soluble. Forms HgCl_2 .	Soluble. Forms HgSO_4 . Ditto.	Soluble. Forms HgSO_4 . Ditto.	Soluble. Forms $\text{Hg}(\text{NO}_3)_2$. Ditto.	Soluble. Forms $\text{Hg}(\text{NO}_3)_2$. Ditto.	Combines easily with organic acids when freshly precipitated.
	Cold. Ditto.	Ditto.					
Nickel	Hot. Soluble. Forms NiCl_2 .	Very slowly soluble. Forms NiCl_2 .	Action slight. Forms NiSO_4 and SO_2 . Practically no action.	Very slowly soluble. Forms NiSO_4 . Ditto.	Easily soluble. Forms $\text{Ni}(\text{NO}_3)_2$ and oxides of nitrogen. Rendered passive.	Easily soluble. Forms $\text{Ni}(\text{NO}_3)_2$ and oxides of nitrogen. Ditto.	
	Cold. Ditto.	Ditto.					
Nickel (-ous) Oxide, NiO.	Hot. Soluble. Forms NiCl_2 .	Soluble. Forms NiCl_2 .	Forms NiSO_4 . Ditto.	Soluble. Forms NiSO_4 . Ditto.	Soluble. Forms $\text{Ni}(\text{NO}_3)_2$. Ditto.	Soluble. Forms $\text{Ni}(\text{NO}_3)_2$. Ditto.	Soluble in NH_4OH .
	Cold. Ditto.	Ditto.					

SUBSTANCE	HYDROCHLORIC ACID		SULPHURIC ACID		NITRIC ACID		REMARKS
	Conc.* Sp. gr. 1.16	Dilute* Sp. gr. 1.048	Conc.* Sp. gr. 1.84	Dilute* Sp. gr. 1.069	Conc.* Sp. gr. 1.42	Dilute† Sp. gr. 1.057	
Nickel (-ic) Oxide, Ni_3O_3 .	Hot. Soluble. Forms NiCl_2 and oxygen. Cold. Ditto.	Soluble. Forms NiCl_2 and oxygen. Ditto.	Forms NiSO_4 . Ditto.	Soluble. Forms NiSO_4 and oxygen. Ditto.	Soluble. Forms $\text{Ni}(\text{NO}_3)_2$ and oxygen. Ditto.	Soluble. Forms $\text{Ni}(\text{NO}_3)_2$ and oxygen. Ditto.	Soluble in NH_4OH with evolution of nitrogen.
Platinum	Hot. No action. Cold. Ditto.	No action. Ditto.	No action. Ditto.	No action. Ditto.	No action. Ditto.	No action. Ditto.	Soluble in Aqua Regia to form PtCl_4 .
Silver	Hot. Practically no action.	Practically no action.	Soluble. Forms Ag_2SO_4 and SO_2 .	Action very slight.	Soluble. Forms AgNO_3 and oxides of nitrogen. Ditto.	Soluble. Forms AgNO_3 and oxides of nitrogen. Action slight.	Finely divided silver is more responsive than compact silver to hydro- chloric acid.
	Cold. Ditto. Hot. Forms AgCl .	Ditto. Forms AgCl .	No action. Soluble: Forms Ag_2SO_4 . Ditto.	No action. Soluble. Forms Ag_2SO_4 . Slightly soluble.	Soluble. Forms AgNO_3 . Ditto.	Soluble. Forms AgNO_3 . Ditto.	Soluble in NH_4OH and KCN solutions.
	Cold. Ditto.	Ditto.					
Tin	Hot. Soluble. Forms SnCl_2 .	Soluble. Forms SnCl_2 .	Dissolves, forming SnSO_4 (stannous sulphate) SO_2 and sulphur. Action slight.	Slowly sol- uble. Forms SnSO_4 .	Forms H_2SnO_3 (metastannic acid), ox- ides of nit- rogen and NH_4NO_3 . Ditto.	Soluble. Forms H_2SnO_3 , $\text{Sn}(\text{NO}_3)_4$ and oxides of nitrogen & NH_4NO_3 . Soluble. Forms $\text{Sn}(\text{NO}_3)_2$, NH_4NO_3 and very little gas.	Soluble in hot concen- trated NaOH or KOH solution. Forms stannates K_2SnO_3 or Na_2SnO_3 .
	Cold. Soluble. Forms SnCl_2 .	Practically no action.		Practically no action.			Aqua Regia in excess dissolves to form stan- nic chloride, SnCl_4 .

SUBSTANCE	HYDROCHLORIC ACID Conc.* Sp. gr. 1·16	Dilute* Sp. gr. 1·048	SULPHURIC ACID Conc.* Sp. gr. 1·84	Dilute* Sp. gr. 1·069	NITRIC ACID Conc.* Sp. gr. 1·42	Dilute† Sp. gr. 1·057	REMARKS
Tin (-ic) Oxide, SnO ₂ .	Hot. No action.	No action.	Slightly soluble.	No action.	No action.	No action.	Slightly soluble in hot conc. NaOH or KOH solutions.
	Cold. Ditto.	Ditto.	No action.	Ditto.	Ditto.	Ditto.	
Tin (-ous) Oxide, SnO.	Hot. Soluble. Forms SnCl ₂ .	Soluble. Forms SnCl ₂ .	Forms SnSO ₄ .	Soluble. Forms SnSO ₄ .	Forms SnO ₂ and oxides of nitrogen. Ditto.	Forms SnO ₂ and oxides of nitrogen. Soluble. Forms Sn(NO ₃) ₂ .	Newth says solution in NaOH is known as sodium stannite.
	Cold. Ditto.	Ditto.	Ditto.	Ditto.			
Zinc	Hot. Soluble. Forms ZnCl ₂ .	Soluble. Forms ZnCl ₂ .	Forms ZnSO ₄ and SO ₂	Soluble. Forms ZnSO ₄ and H, and, if not sufficiently diluted, H ₂ S.	Soluble. Forms Zn(NO ₃) ₂ , oxides of nitrogen and NH ₄ NO ₃ .	Soluble. Forms Zn(NO ₃) ₂ , oxides of nitrogen and NH ₄ NO ₃ .	Soluble in hot concentrated KOH and NaOH solutions.
	Cold. Ditto.	Ditto.	Forms ZnSO ₄ .	Soluble. Forms ZnSO ₄ and H.	Soluble.	Soluble.	
Zinc Oxide, ZnO.	Hot. Soluble. Forms ZnCl ₂ .	Ditto.	Slightly soluble. Forms ZnSO ₄ .	Soluble. Forms ZnSO ₄ .	Soluble. Forms Zn(NO ₃) ₂ .	Soluble. Forms Zn(NO ₃) ₂ .	Soluble in NH ₄ Cl, NaOH and KOH solutions.
	Cold. Ditto.	Ditto.	Ditto.	Ditto.	Ditto.	Ditto.	

SOME ORGANIC REAGENTS FOR INORGANIC ANALYSIS

During recent years increasing use has been made of various organic compounds for the identification, and often for the determination, of metallic radicles even when present in very minute proportion. The following pages contain information as to the methods of using some of the more important of these reagents. In the majority of cases the qualitative tests may be applied by the "Spot" method of Prof. Feigl, the test solution being "spotted" on to blotting-paper by means of a capillary tube, and the reagent then applied to the spot in the same way. The "Spot" technique is particularly useful when only a very small amount of material is available for analysis. For further details as to the methods of using the reagents, and preventing interference from ions other than those for which the tests are intended, reference may be made to *Organic Reagents for Metals* (Hopkin and Williams) from which most of the following particulars are taken, or to *Reagents for Spot Tests* (B.D.H.). The former publication contains a comprehensive bibliography. Fuller information is contained in *Qualitative Analyse mit Hilfe von Tüpfelreaktionen*, by Dr. Fritz Feigl.

Ammonium Aurine-tricarboxylate. *Syn.* ALUMINON. $(C_6H_3 \cdot OH \cdot COONH_4)_2 : C : C_6H_3(COONH_4) : O$.

For the detection and determination of aluminium. The reagent is used as a 0.1% solution in water. To the solution to be tested, evaporated to about 5 ml. and acidified slightly with hydrochloric acid, is added 5 ml. of 25% *w/v* ammonium acetate solution and an equal volume of the reagent solution. In the presence of aluminium a red colouration or precipitate is produced on allowing to stand for 5 minutes. The colour is reduced in intensity if ammonium carbonate solution be added. The solution to be tested must be free from iron, and excess of alkaline earth metals must be avoided. The test may also be used quantitatively.

Ammonium Nitrosophenylhydroxylamine. *Syn.* CUPFERRON. $C_6H_5N(NO)ONH_4$.

For the determination of iron, titanium or zirconium. The reagent is used as a 5% solution in water, and should be filtered if necessary. The reagent becomes dark-coloured on long storage, and the solution also gradually becomes darker but keeps satisfactorily for several days.

For iron. The solution containing about 0.1 g. of iron in 150 ml. to 200 ml. is strongly acidified with hydrochloric acid, and the reagent solution added with constant stirring until a white precipitate of nitrosophenylhydroxylamine begins to form. The brownish-red precipitate of the iron compound is collected, washed several times with dilute hydrochloric acid containing a few drops of the reagent, then with diluted ammonia solution (5% *w/v* of NH_3) to remove excess cupferron, and finally ignited. Each gramme of F_2O_3 is equivalent to 0.699 g. of Fe.

Titanium or zirconium. The precipitation of these metals is carried out in the same way, except that the test solution should contain about 0.05 g. in 150 ml. to 200 ml. and the precipitate is washed thoroughly with dilute hydrochloric acid containing a little cupferron, no ammonia being used. The precipitate is ignited, gently at first but afterwards more strongly, to TiO_2 . Each gramme of TiO_2 is equivalent to 0.60 g. of Ti. Precipitation in each case from a strongly acid solution prevents interference from Al, Cr, Mn, Ni, Co, Zn, Mg, and the alkali and alkaline earth metals. Metals of the copper group should be removed by means of hydrogen sulphide before treatment with cupferron. When determining titanium or zirconium, iron must be removed by reduction with hydrogen sulphide and precipitation with ammonia in tartrate solution.

α -Benzoin Oxime. *Syn.* CUPRON. $C_6H_5 \cdot CHOH \cdot C : NOH \cdot C_6H_5$.

For the detection and determination of copper. The reagent is used as a 1% solution in alcohol. To 20 ml. of the solution to be tested are added a small quantity of sodium potassium tartrate solution and 1 ml. of the reagent. In the presence of copper a green precipitate is produced either at once or after some hours, according to the proportion present. In the absence of tartrate ions precipitates are also given by Co, Ni, Pb, Fe, and Al.

For the determination of copper, the test solution, containing not more than 0.05 g. of copper, is treated with excess of solution of ammonia, raised to the boiling-point, and then treated with a slight excess (about 5 ml.) of a 4% alcoholic solution of the reagent. The precipitate is washed free from soluble salts with hot 1% ammonia solution, and then hot alcohol to remove excess of the reagent. The precipitate is dried to constant weight at 110° . Each gramme of residue is equivalent to 0.2202 g. of Cu. In the presence of any interfering element, a solution of sodium potassium tartrate must be added to the test solution.

***o*-*p*-Dihydroxybenzeneazo-*p*-nitrobenzene.** *Syn.* MAGNESON; *o*-*p*-Dihydroxyazo-*p*-nitrobenzene; *p*-Nitrobenzeneazoresorcinol. $NO_2 \cdot C_6H_4N : NC_6H_3(OH)_2$.

For the detection of magnesium. The reagent is used as a 0.1% solution in 1% sodium hydroxide solution; it keeps for several months but should not be used if more than a year old. The test solution is freed from other metallic radicles except the alkali metals by the ordinary group reactions. Ammonium compounds are then removed by evaporating to dryness and igniting. The residue is dissolved in 10 ml. of water acidified with hydrochloric acid, and 1 drop of the reagent is added, followed by 10 ml. of sodium hydroxide solution. A blue colour or precipitate visible after about 5 minutes denotes the presence of Mg.

Dihydroxytartaric Acid. $[(HO)_2C \cdot COOH]_2$.

For the detection and determination of sodium. The reagent is used as a solution of its potassium salt prepared by neutralising until slightly pink a solution of 1 g. of the acid in 20 ml. of water containing 1 drop of phenolphthalein solution and cooled in ice, with N/1 KOH, also cooled in ice. The solution should not be kept for more than 1 day. The solution to be tested is cooled below 5° and mixed with an equal volume of the reagent solution. The mixture is allowed to stand below 5° . In the presence of sodium a white crystalline precipitate forms in from 1 minute to several hours according to the proportion present.

For the determination of sodium. 10 ml. of a solution containing about 0.03 g. of Na is precipitated as described, and the mixture is allowed to stand overnight at 0° to 5° . The precipitate is washed with a total volume of 10 ml. of ice-cold water and then dissolved in 10 ml. of warm 5N sulphuric acid, the filter being thoroughly washed with water, and the washings added to the solution. The sodium may now be determined either volumetrically or gravimetrically. In the former case the solution is acidified further with 5 ml. of concentrated sulphuric acid and titrated at 80° with N/10 potassium permanganate until the pink colour persists for 1 minute. Each millilitre of N/10 potassium permanganate is equivalent to 0.000767 g. of Na. The gravimetric determination is completed by evaporation to dryness and ignition to constant weight in a platinum basin. Each gramme of residue, Na_2SO_4 , is equivalent to 0.324 g. of Na.

***p*-Dimethylaminobenzylidenerhodanine.**

For the detection of silver. The reagent is used as a 0.03% solution in acetone. To 20 ml. of the approximately neutral test solution add 2 ml. of N/1 nitric acid and 0.5 ml. of the reagent. The presence of silver is denoted by the production of a reddish coloration. In the presence of mercuric compounds 0.5 ml. of N/1 hydrochloric acid must be added after the reagent. In the presence of gold, platinum or palladium 0.5 ml. of 10% potassium cyanide solution must be added to the test solution, followed by the reagent and then the nitric acid. If copper is present, it must be oxidised to the cupric state, no coloration being then produced in acid solution. Cuprous ions give a violet precipitate or coloration.

Dimethylglyoxime. *Syn.* DIACETYLDIOXIME. $CH_3 \cdot C : (NOH) \cdot C : (NOH) \cdot CH_3$.

For the detection and determination of nickel. The reagent is used as a 1% solution in alcohol. A few drops of the reagent solution are added to the boiling acidified test solution, and the mixture is then rendered alkaline by solution of

ammonia. In the presence of nickel, red needles are produced. In the presence of a large excess of cobalt (for example, in testing for nickel in cobalt compounds), ammonia solution is added to the test solution until clear; and followed by a little hydrogen peroxide, the excess being removed by boiling. The reagent solution is then added and the liquid filtered. If nickel is present, the red precipitate can be observed on the filter paper.

For the determination of nickel, the test solution should contain not more than 0.1 g. of Ni in 200 ml. After precipitation as above, the crystals are filtered off after 1 hour, washed with hot water and dried at 115° for 45 minutes. Each gramme of residue, $(C_4H_7O_2N_2)_2Ni$, is equivalent to 0.2032 g. of Ni. The reagent may also be used for the *detection of bismuth*. An acid solution containing bismuth and a chloride is treated with a few drops of the reagent and the mixture made strongly alkaline with ammonia solution. In the presence of bismuth an intense yellow precipitate or coloration is produced according to the proportion present. The reaction does not take place in the presence of an excess of tartrate, and by utilising this, nickel may be tested for in bismuth.

Diphenylcarbazone. $C_6H_5 \cdot NH \cdot NH \cdot CO \cdot N : N \cdot C_6H_5$.

For the detection of mercury. The reagent is used as a saturated solution in alcohol. The test solution is rendered neutral or very faintly alkaline by the addition of sodium acetate (about 1 g. of sodium acetate per 10 ml. of solution is usually sufficient), and 1 drop of reagent per 10 ml. of solution is added. In the presence of mercury a violet or blue colouration is produced. The sensitivity of the reaction is greatly decreased if halides or cyanides be present in considerable quantity. Pb, Cu, Sn, Cd, Ni and Co interfere if only traces of Hg are present. In the case of an organic compound the substance is boiled with hydrochloric acid and potassium chlorate, and pieces of zinc are placed in the solution for 4 hours. The zinc is treated with chlorine water and the test is applied to the washings.

8-Hydroxyquinoline. *Syn.* OXINE. $C_9H_6N \cdot OH$.

For the determination of magnesium, zinc and aluminium. The reagent is used either as a 5% solution in alcohol or as a solution in dilute acetic acid prepared by dissolving 2 g. of the reagent in 100 ml. of 2N acetic acid and adding solution of ammonia until a slight permanent precipitate is produced.

Determination of magnesium. The test solution, containing about 0.02 g. of magnesium in 50 ml., is made alkaline with ammonia, sufficient ammonium chloride being added to prevent precipitation, and heated nearly to the boiling-point. The alcoholic reagent solution is then added until the liquid becomes yellow in colour, when a compound of the composition, $Mg(C_9H_6ON)_2 \cdot 4H_2O$ separates. The precipitate is collected, washed with hot faintly ammoniacal water and dried at 100° to 105° , at which temperature $2H_2O$ is lost. Each gramme of residue is equivalent to 0.0698 g. of Mg. Alternatively, the precipitate may be dissolved in 5N hydrochloric acid, and the filter washed with sufficient water to yield 2N acid. The solution is titrated to a yellow with N/5 bromine solution, using methyl red as indicator. Potassium iodide is added and the liberated iodine titrated with N/10 sodium thiosulphate. Each millilitre of N/5 bromine is equivalent to 0.000608 g. of Mg. Direct titration with N/5 bromine is impracticable because of the indefinite end-point.

Determination of zinc. To the test solution, which should be slightly acid and should contain about 0.05 g. of Zn in 50 ml., is added 3 g. to 5 g. of sodium acetate. After warming to 60° to 70° the zinc is precipitated by the addition of excess of the alcoholic 8-hydroxyquinoline solution. The precipitate is collected, washed and dried. If dried at 100° , the composition is $Zn(C_9H_6ON)_2 \cdot 1\frac{1}{2}H_2O$ which contains 17.18% of zinc; at 120° to 130° the crystals become anhydrous, and then contain 18.50% of Zn. The precipitate may also be determined volumetrically as described for magnesium. Each millilitre of N/5 bromine is equivalent to 0.001635 g. of Zn.

Determination of aluminium. The slightly acid test solution containing about 0.02 g. of Al per 100 ml. is precipitated by the addition of the acetic 8-hydroxyquinoline solution. The mineral acid is neutralised with ammonium acetate, the solution cooled and the precipitate collected, washed with water, acidified with acetic acid, and dried at 110° . The residue, $Al(C_9H_6ON)_3$, contains 5.87% of Al. The precipitate may also be determined volumetrically as described for magnesium, after solution in concentrated hydrochloric acid and dilution with about 5 times the volume of water. Each millilitre of N/5 bromine is equivalent to 0.0004495 g. of Al.

Picrolonic Acid. *Syn.* 1-*p*-Nitrophenyl-3-methyl-4-nitro-pyrazolone-5.

For the detection of copper and lead, and the detection and determination of calcium. The reagent is used as a 0.25% aqueous solution.

For the detection of copper, lead and calcium. To the neutral test solution add an equal volume of the reagent solution. Each of the three metals produces a yellow precipitate.

Determination of calcium. To the hot neutral test solution containing not more than 0.1 g. of calcium, add a solution of 2 g. of the reagent in 750 ml. of hot water. Allow to stand overnight, filter on a tared sintered glass crucible, wash, and dry to constant weight by drawing air through the filter. Each gramme of precipitate is equivalent to 0.05642 g. of Ca.

Picrolonic acid is also used for the identification of organic bases with which in alcohol solutions, it gives precipitates. The picrolonates are easily crystallisable and give sharp melting-points.

Salicylaldoxime. $C_6H_4 \cdot OH \cdot CH : NOH$.

For the detection and determination of copper. The reagent is used as a solution obtained by dissolving 1 g. in 5 ml. of alcohol and diluting to 100 ml. with water. The test solution is acidified with acetic acid and one-twentieth of its volume of the reagent solution is added. In the presence of copper an immediate precipitate is produced.

Determination of copper. The test solution, containing not more than 0.1 g. of copper, is treated with sodium hydroxide solution until a precipitate appears and is then acidified with acetic acid. 50 ml. of the reagent solution is added and the liquid is stirred to coagulate the precipitate, and filtered. The precipitate is washed with cold water and dried to constant weight at 100° to 105°. Each gramme of precipitate is equivalent to 0.1894 g. of Cu.

Zinc Uranyl Acetate

For the detection and determination of sodium. The solution of the reagent is obtained by mixing a solution of 10 g. of uranyl acetate in 6 g. of acetic acid and 65 g. of hot water with a solution of 30 g. of zinc acetate in 3 g. of acetic acid and 65 g. of hot water. The mixed liquids are maintained at 19° to 21° for several hours and any crystals of the triple salt, $NaZn(UO_2)_3(C_2H_3O_2)_9 \cdot 6H_2O$, are removed by filtration.

For the detection of sodium. The test solution is neutralised and mixed with an equal volume of the reagent. In the presence of sodium yellow crystals of sodium zinc uranyl acetate are produced.

For the determination of sodium. To 10 ml. of the neutral solution containing not more than 0.08 g. of sodium is added 100 ml. of the reagent, and the mixture is allowed to stand at 19° to 21° for 30 to 45 minutes with occasional stirring. The crystals are collected, washed with five successive quantities each of 2 ml. of the reagent and then with five successive quantities each of 2 ml. of alcohol saturated at 20° with sodium zinc uranyl acetate. The precipitate is washed finally with ether, dried at 40° for 10 to 15 minutes and weighed. Each gramme of precipitate is equivalent to 0.01495 g. of sodium.

INDICATORS

The following indicators are those most generally used for volumetric analysis and for the colorimetric determination of the hydrogen ion concentration of solutions.

INDICATOR	COLOUR CHANGE	STRENGTH AND SOLVENT	REMARKS
Alkali Blue <i>Syn.</i> Nicholson's Blue. A mixture of the sodium sulphonates of phenylated rosaniline and para-rosaniline	From blue to red with strong alkali in alcoholic solution	0.1% in alcohol (90%)	Used in the alkali limit test of the <i>B.P.</i> for Liquor Cresolis Saponatus.
Bromocresol Green (Tetra-bromo- <i>m</i> -cresolsulphonephthalein)	*pH 3.6 yellow pH 5.2 blue	0.1 g. warmed with 2.9 ml. of N/20 NaOH and 5 ml. of alcohol (90%) until dissolved and diluted with alcohol (20%) to 250 ml.	Used for titrating phosphoric acid and disodium phosphate. Gives a green colour at pH 4.5 which corresponds to the formation of sodium acid phosphate.
Bromocresol Purple (Dibromo- <i>o</i> -cresol-sulphonephthalein)	pH 5.2 yellow pH 6.8 purple	0.1 g. warmed with 3.7 ml. of N/20 NaOH and 5 ml. of alcohol (90%) until dissolved, and diluted with alcohol (20%) to 250 ml.	"This is the most trustworthy indicator for quinine."— <i>J. Amer. chem. Soc.</i> , 1922, 2156. Used for determination of the pH of solutions.
Bromophenol Blue (Tetra-bromo-phenol-sulphonephthalein)	pH 2.8 yellow pH 4.6 purple	0.1 g. warmed with 3 ml. of N/20 NaOH and 5 ml. of alcohol (90%) until dissolved and diluted with alcohol (20%) to 250 ml.	Methyl red, methyl orange or cochineal give low results for morphine, while bromophenol blue gives a satisfactory value and end-point. This is also true for atropine and mydriatic residues.— <i>J. chem. Soc. Abstr.</i> , ii/1922, 885; also <i>Pharm. J.</i> , i/1921, 470. Used for pH determinations.

*pH 3.6 means a hydrogen ion concentration of $10^{-3.6}$ g. per litre (see p. 225), when bromocresol green is yellow. The addition of alkali to lower the hydrogen concentration to 10^{-7} changes the colour. Thus with acids this indicator is yellow and with alkalis purple.

INDICATOR	COLOUR CHANGE	STRENGTH AND SOLVENT	REMARKS
Bromo-thymol Blue (Dibromo-thymol-sulphone-phthalein)	pH 6 yellow pH 7·6 blue	0·1 g. warmed with 3·2 ml. of N/20 NaOH and 5 ml. of alcohol (90%) until dissolved, and diluted with alcohol (20%) to 250 ml.	Used for determination of the pH of solutions.
Cochineal	pH 0—4 yellow pH 5 brown-pink pH 6 purple	<i>B.P.</i> employs the tincture (1 in 10)	Useless for organic acids. Sharp end-reaction with inorganic acids and bases by back titration. Suitable for solutions of the alkaline earths. Used for titrating alkaloids with mineral acids, but end-point not sharp. Cannot be used in presence of acetates or compounds of Fe or Al.
Congo Red (Sodium diphenyl-bisazobis-naphthyl-amine-4-sulphonate)	pH 3 blue pH 4 violet pH 5 scarlet	0·5% in alcohol (25%)	Responds well to inorganic acids and inorganic bases. Responds to organic bases, but not good for titrating, e.g., quinine or atropine.
Cresol Red (<i>o</i> -cresol-sulphone-phthalein)	pH 7·2 yellow pH 8·8 red	0·05 g. warmed with 2·65 ml. of N/20 NaOH and 5 ml. of alcohol (90%) until dissolved and diluted with alcohol (20%) to 250 ml.	Used for the determination of the pH of solutions.
Hæmatoxylin	Yellow with acids to green or purple with alkalis	1% in alcohol (90%)	Responds to inorganic and organic acids. Responds to inorganic bases, and to organic, e.g., alkaloids. Occasionally used in alkaloidal titrations, e.g., quinine residues, yielding good end-points.
Dimethyl Yellow (Dimethyl-aminoazo-benzene)	pH 2·4 red pH 4 yellow	0·2% in alcohol (90%)	

INDICATOR	COLOUR CHANGE	STRENGTH AND SOLVENT	REMARKS
Iodo-Eosin (Tetraiodo-fluorescein)	Red with alkalis in aqueous solution, yellow with acids in ether layer	0.1% in alcohol (90%). 0.01% in water. Sometimes 0.01% in ether is used	Used for titrating minute quantities of alkali with N/100 or N/1000 acid and for small quantities of alkaloids which are alkaline to it. In use 10 ml. to 20 ml. of ether are added to the titration flask to form a layer above the liquid. Alkalis produce a red in the aqueous layer and acids a yellow in the ether layer. It is a poor indicator, e.g., with strychnine. Not suitable for ordinary titrations.
Lacmoid	pH 0—4 pink pH 5 violet pH 7 blue These changes are not sharp	0.2% in alcohol (60%)	This indicator is somewhat less sensitive to CO ₂ than litmus, and is used similarly.
Litmus	pH 5 red pH 8 blue	Boil 10 g. for 1 hour with 40 ml. of alcohol (90%) and pour off the clear liquid; repeat the boiling, etc., twice with 30 ml. of alcohol (90%). Digest the washed litmus with 100 ml. of water and filter	CO ₂ if present must be removed by boiling. Suitable for inorganic acids and for lactic, oxalic and tartaric acids. Not suitable for weak acids and alkalis. Quinine, morphine and strychnine are neutral to it. The acid in their salts can be titrated, using litmus, as though no base were present.— <i>Pharm. J.</i> , i/1915, 135. The end-points are not good.
Methyl Orange	pH 2.8 red pH 5 yellow	0.04% in alcohol (20%)	Suitable for titrating strong mineral acids but cannot be used for organic acids. Alkaloids are alkaline to it, but end-point not good, e.g., in case of quinine. Alkali carbonates and bicarbonates can be titrated without boiling as this indicator is unaffected by CO ₂ . Should not be used in alcoholic or boiling solutions. Acid phosphates, e.g., NaH ₂ PO ₄ , are neutral to methyl orange.

INDICATOR	COLOUR CHANGE	STRENGTH AND SOLVENT	REMARKS
Methyl Red (<i>p</i> -Dimethyl-aminoazo-benzene- <i>o</i> -carboxylic acid)	<i>pH</i> 4·2 red <i>pH</i> 6·3 yellow	0·025 g. warmed with 0·95 ml. of N/20 NaOH and 5 ml. of alcohol (90%) until dissolved and diluted with alcohol (25%) to 250 ml.	Is more sensitive than methyl orange and the colour change is sharper, but it is more sensitive to CO ₂ which must be removed by boiling. It is suitable for titrating ammonia or alkalis but not for weak organic acids. Used for determination of the <i>pH</i> of solutions.
Naphthol-phthalein	<i>pH</i> 7·3 colourless <i>pH</i> 8·7 blue	0·1% in alcohol	Used for determination of the <i>pH</i> of solutions.
Phenolphthalein	<i>pH</i> 8·3 colourless <i>pH</i> 10 red	0·2 g. dissolved in 60 ml. of alcohol (90%) and diluted with water to 100 ml.	Usually employed for titrating inorganic and organic acids, and may be used in alcoholic or hot solutions. Some organic bases, e.g., the alkaloids atropine, are alkaline to this indicator but morphine, quinine and strychnine are not. Phenolphthalein must not be used in presence of ammonia or its salts, and is affected by CO ₂ .
Phenol Red	<i>pH</i> 6·8 yellow <i>pH</i> 8·4 red	0·05 g. warmed with 2·85 ml. of N/20 NaOH and 5 ml. of alcohol (90%) until dissolved and diluted with alcohol (20%) to 250 ml.	Used for titrating weak organic acids such as benzoic and salicylic. Used for determination of the <i>pH</i> of solutions. It is employed in this way for blood, and in media to differentiate typhoid and paratyphoid bacilli, <i>q.v.</i>
Phenol Violet	<i>pH</i> 8 yellow through blue to <i>pH</i> 10 violet	0·15 g. of thymol blue and 0·025 g. of phenolphthalein warmed with 3·25 ml. of N/10 NaOH and 5 ml. of alcohol (90%) until dissolved, and diluted with alcohol (20%) to 250 ml.	Used as an alternative to phenolphthalein in the titration of boric acid.

INDICATOR	COLOUR CHANGE	STRENGTH AND SOLVENT	REMARKS
Potassium Chromate	Red colour due to formation of silver chromate, occurring only after halide is all precipitated	1 in 20 of water. A few drops of the solution are employed	For titrating soluble halides with silver nitrate. The solution of the halide must be neutral, since silver chromate is soluble in acid.
Potassium Ferrocyanide	When blue or green coloration is no longer produced	5% solution in water, to be freshly made. Drops of it or a few small crystals are placed on a white tile	Employed for titrating ferrous iron with potassium dichromate. Also used in titrating phosphate or arsenate with uranium acetate solution. In this case the end-point is the <i>appearance</i> of a brown colour on the ferrocyanide crystal (after boiling the solution) due to formation of uranium ferrocyanide.
Rosolic Acid <i>Syn. Corallin, Aurin</i>	pH 6 yellow pH 7 pink pH 8 red	0.5% in alcohol (50%)	Responds to inorganic bases and to organic bases. Not suitable for use in presence of ammonia or CO ₂ . End-point not very sharp.
Starch	Formation or disappearance of blue colour	0.5% in water, boiled and cooled	For use in the titration of oxidisable substances, e.g., arsenious acid or thio-sulphate, with iodine or <i>vice versa</i> .
Thymol Blue (Thymol-sulphone-phthalein)	pH 1.2 red pH 2.8 yellow pH 8 greenish-yellow pH 9.6 blue	0.1 g. warmed with 4.3 ml. of N/20 NaOH and 5 ml. of alcohol (90%) until dissolved, and diluted with alcohol (20%) to 250 ml.	In the alkaline range it gives a sharper end-point than phenolphthalein and is used in the titration of citric acid. Used also for determination of the pH of solutions.
Thymol Phthalein	pH 8 colourless pH 10 blue	0.04% in alcohol (60%)	Used for determination of the pH of solutions.
Turmeric	Orange red with alkalis, yellow with acids	10 g. macerated with 60 ml. of alcohol (90%) for 7 days and filtered	Responds to inorganic or organic acids and bases. Requires daylight. Not very satisfactory for alkalis, except atropine. Suitable for estimating boric acid. Sensitive to ammonia (1 in 35,000) and potash (1 in 180,000).

The use of some other types of indicators is dealt with in a lecture by Dr. A. D. Mitchell to the Institute of Chemistry (October 19th, 1934). The following are some examples mentioned.

Mixed Indicators

By suitably mixing different indicators, mixed indicators can be prepared to have sharp colour changes over selected narrow ranges of pH .

A mixture of **equal parts of neutral red and methylene blue** changes from violet-blue to green (from acid to alkaline solution) at pH 7. It may be used for the titration of a weak acid with a weak base.

A mixture of **α -naphtholphthalein**, 1 part, and **phenolphthalein** 2 parts changes from pale rose through green to violet at pH 9.6, and can be used for titrating phosphoric acid to the dibasic stage.

A mixture of **thymol blue**, 6 parts, and **cresol red**, 1 part, changes from rose at pH 8.2, through blue at pH 8.3 to violet at pH 8.4, and can be used for titrating carbonates to the bicarbonate stage.

Fluorescent Indicators

Certain substances when exposed to ultra-violet light show fluorescence only in solutions having a limited range of pH , and if this range covers the point of neutrality the occurrence of fluorescence can be used as an indicator. These indicators are valuable for the titration of strongly coloured liquids.

Umbelliferone develops a sky-blue fluorescence as the pH changes from 6.5 to 7.6.

Quinine gives a fluorescence at pH 6 and at pH 9.5 to 10.0. The former change can be used for titrating strong acids in dilute solution.

Oxidation-Reduction Indicators

These depend for their colour not upon the absolute concentration of a particular ion such as the hydron but upon the ratio of the concentration of two ions, one corresponding to a high stage of oxidation of the other.

Diphenylamine is not oxidised by permanganate in the presence of ferrocyanide until the ratio ferricyanide/ferrocyanide is greater than a certain value at which practically the whole of the ferrocyanide has been oxidised. In using diphenylamine the ferrocyanide solution is acidified with sulphuric acid until the acidity is slightly more than normal and a few drops of a 1% solution of the indicator in sulphuric acid are added. The completion of the titration is shown by the development of a violet colour.

Diphenylamine may also be used as internal indicator in the titration of ferrous salts with dichromate. The ferrous ion solution is acidified to about $N/2$ or $N/10$ with sulphuric or hydrochloric acid, 2 ml. to 3 ml. of phosphoric acid is added together with a few drops of indicator solution. Titration is continued to the production of an intense violet colour.

Adsorption Indicators

These are coloured compounds which at the completion of the reaction are adsorbed upon the precipitate produced in a titration, forming a complex with a colour distinct from that of the solution.

Fluorescein (1 mg. per litre of the liquid being titrated) may be used in the titration of a chloride with silver nitrate. Completion of the titration is indicated by the formation of a pink colour on the precipitate, the solution being greenish yellow. The chloride solution should be neutral or faintly acidified with acetic acid and not more dilute than $N/100$.

Dichlorofluorescein may be used similarly for chlorides in great dilution and in the presence of acetic acid.

Eosin, 10 mg. per litre, may be used for titrating bromides even in great dilution or in $N/10$ nitric acid. The precipitate acquires a magenta colour, the liquid being red.

Di-iodomethylfluorescein (5 to 10 drops of 1% solution per 100 ml.) is better than eosin for titrating iodides, the colour of the precipitate being blue-red, of the solution orange-red. It may be used in the presence of small amounts of chloride.

Diphenylcarbazine may be used for cyanide, the pink colour of the liquid becoming pale violet (almost colourless) on the colloidal precipitate before its precipitation is visible.

THE DETERMINATION OF THE HYDROGEN ION CONCENTRATION OF SOLUTIONS

Theoretical Notes

A solution is acid when it contains an excess of hydrogen over hydroxylions, neutral when they are in equal numbers, alkaline when hydroxylions predominate, the product of the concentrations, $(H) \times (OH)$, in water being always constant at the same temperature ($10^{-14.14}$ at $18^\circ C.$).

An acid of "normal" strength contains in 1 litre 1 g. of hydrogen capable of forming hydrogenions, and its strength may be viewed as N/1. Pure water, however, dissociates to form hydrogen and hydroxylions and at 20° contains approximately 10,000,000 g. of hydrogenions to the litre and an equivalent amount of hydroxylions. That is to say, pure water, our standard of neutrality, is 1/10,000,000 N acid and also 1/10,000,000 N alkaline. For brevity this fraction may be expressed 10^{-7} N. Sørensen suggested dropping the 10 and the minus sign and calling it pH 7. pH is therefore $-\log (H)$. If there is less than 10,000,000 g. of hydrogen-ions in 1 litre, the solution is less acid than water, i.e., it is alkaline—so pH 8 means 1/1,000,000 N alkali, and similarly pH 14 is N/1 alkali.

To conclude:

pH 1 = N/10 acid.

pH 6 = N/1,000,000 acid.

pH 7 = NEUTRALITY.

pH 8 = N/1,000,000 alkali.

pH 14 = N/1 alkali.

The Use of Indicators

For dark coloured solutions and for exact determinations of pH an electro-metric method is used but has the disadvantage of requiring complicated apparatus. However, for most practical purposes the colorimetric method, using indicators, is sufficiently accurate and is easily carried out. This process depends on the fact that every indicator changes colour over a definite zone of pH, suitable indicators being thymol blue, bromophenol blue, methyl red, m-cresol purple, bromothymol blue, phenol red, and thymolphthalein.

The method consists in testing the solution with various indicators (5 drops per 10 ml. of solution) until one is found which gives a tint lying between its extremes of colour. This gives an approximate value for the pH of the solution, and for more exact estimation the tint obtained is compared with that given by solutions of known pH and the same indicator until an exact match is observed. Details of suitable buffer solutions are given by N. Evers (*Analyst*, 1921, 393), or in Appendix iii of the *B.P.* '32.

A Universal Indicator and Buffer Solution.

When the approximate pH of the solution only is required this can rapidly be ascertained by the use of a mixed or universal indicator which gives a series of colours at different values of pH . A Universal Indicator can be prepared by dissolving methyl orange 0.04 g., methyl red 0.02 g., naphtholphthalein 0.18 g. and phenolphthalein 0.08 g. in 100 ml. of 70% alcohol, and this gives the whole range of spectrum colours in the correct order from red (pH 3) to violet (pH 11). The hydron concentration of a solution is found by adding 5 drops of this indicator to 10 ml. and from the colour obtained the value of the pH can be read off from the table below, but it is better to compare the tint with that given by solutions of known pH . For such solutions it is convenient to use the Universal Buffer Mixture proposed by E. B. R. Prideaux and A. T. Ward (*J. chem. Soc.* 1924, 426), which gives solutions of definite pH from 2 to 12 by neutralising a caustic soda solution. This solution contains H_3PO_4 1.961 g., phenylacetic acid 2.722 g., and boric acid 1.238 g. in 500 ml., and for use 10 ml. is mixed with the requisite amount of $N/5$ NaOH and made up to 20 ml. The final solution is $N/10$ with respect to each hydron, the whole being $N/10$.

The volume of $N/5$ NaOH required for some pH values is shown in the table below, for intermediate values the graph in the original paper (*loc. cit.*) must be consulted. The formula $pH = 0.773 + 1.185 V$, where $V = \text{ml. } N/5 \text{ NaOH}$ in 10 ml. of solution, is sufficiently accurate for many purposes, and holds between $V = 1.5$ ml. and $V = 9$ ml. The colour changes of the universal indicator at the composition of the universal buffer solution with different values of hydron concentration are also shown:—

APPROX. VALUE OF pH	ML. $N/5$ NaOH PER 10 ML. BUFFER SOLUTION in 20 ML.	COLOUR WITH UNIVERSAL INDICATOR (5 DROPS PER 10 ml.)	APPROX. VALUE OF pH .	ML. $N/5$ NaOH PER 10 ML. BUFFER SOLUTION in 20 ML.	COLOUR WITH UNIVERSAL INDICATOR (5 DROPS PER 10 ml. SOLUTION)
2.0	0.0	—	7.5	5.6	yellowish-green
3.0	2.0	crimson	8.0	6.0	green
4.0	2.8	red	8.5	6.2	bluish-green
5.0	3.6	orange-red	9.0	7	greenish-blue
5.5	4.0	orange	9.5	7.3	blue
6.0	4.5	orange-yellow	10.0	7.7	violet
6.5	4.8	yellow	11.0	8.5	reddish-violet
7.0	5.2	greenish-yellow	12.0	10.0	—

Methyl Orange. The colour change is made more readily detectable by the addition of 1.4 g. of xylene-cyanole FF to 1 g. of the indicator in 500 ml. of alcohol (50%). Colour change is from green in alkaline solution to magenta in acid solution, with a neutral grey at pH 3.8.—Hickman and Linstead, *J. chem. Soc.*, 1922, 2501.

Methylene Blue may be used as internal indicator in the titration of Fehling's solution with sugar solutions. The bulk of the sugar solution estimated to be required is added rapidly, and a few drops of 1% methylene blue towards the end of the titration. The blue colour disappears accurately at the end-point.—Linstead and Eynon, *J. Soc. chem. Ind.*, 1923, 42, 32T.

Bromophenol-blue—indicator corrections for temperature and presence of alcohol.—*J. chem. Soc. Abstr.*, ii/1925, 237.

Carbonate Titrations.—A mixture of cresol red and thymol blue gives a sharp end-point, corresponding approximately to the half-neutralisation.

at, and then the addition of bromophenol blue gives a sharp change from e to green on complete neutralisation.—*J. chem. Soc. Abstr.*, ii/1924, 627; *Pharm. J.*, i/1925, 8.

A mixture of equal parts of 1% alcoholic solutions of neutral red and phenol forms an indicator which shows a sharp change of colour at point of real trality, and is efficient for the titration of very weak acids and bases, but is sensitive to carbon dioxide.—*J. chem. Soc. Abstr.*, ii/1925, 899.

A Universal Indicator, having a range from pH 3.5 to 7.6, and suitable for in soil experiments, consists of a mixture of alcoholic solutions of 0.04% bromophenol blue (4 vols.), 0.04% bromocresol purple (1 vol.), 0.02% methyl (6 vols.), and 0.04% bromothymol blue (4 vols.).—*J. chem. Soc. Abstr.*, 1925, 348.

Chlorides may be titrated accurately in any acid solution using potassium omate provided that the pH value is first reduced to between 5 and 7 by addition of a sodium acetate acetic-acid (2 mols : 1) buffer mixture.—*J. chem. Soc. Abstr.*, ii/1925, 238.

Alkaloids. In the titration of alkaloids by solution in excess of acid and alk titration with alkali, the following indicators are recommended. They based on the use of a solution containing 0.1 g. of the alkaloid in 50 ml.

METHYL RED recommended for titration of aconitine, atropine, brucine, haëline, codeine, cocaine, diamorphine, emetine, ethylmorphine, homa-pine, hyoscyamine, morphine, nicotine, physostigmine, strychnine, thebaine and yohimbine.

BROMOCRESOL PURPLE for cinchonine, cinchonidine, cotarnine, ethylhydro-reine, quinine and quinidine.

BROMOPHENOL BLUE for delcosine, narceine, narcotine and pilocarpine.—*Analyst*, 1926, 316.

Distilled Water, pH value of, obtained as pH 6.7 to 6.6, using dilute methyl and neutralised with sodium hydroxide colorimetrically.—*Brit. chem. Abstr.*, 1928, 03.

A buffer mixture of succinic acid and borax for pH values 3.0 to 5.8, and of ccinic acid and potassium hydrogen phosphate for values of 5.8 to 9.2.—*biol. Chem.*, 1925, 135.

Hydrogen-ion control. A useful summary. It is pointed out that as the ion concentration of N/10 HCl is 0.0914 g. per litre and that of N/10 acetic d 0.00136 g. per litre the HCl contains almost 70 times as many H-ions as e acetic acid.—W. A. Taylor, *Pharm. J.*, i/1928, 31.

SCHEME FOR THE RECOGNITION OF ORGANIC CHEMICAL SUBSTANCES USED IN THERAPEUTICS

The following scheme is intended to assist in the recognition of a number of organic chemicals, both natural and synthetic, used therapeutically. It frequently happens that the analyst is called upon to identify such substances, and without some guide the search is sometimes extremely difficult.

The Preliminary Tests are first carried out, and by comparison of the results with the tables, some idea of the nature of the substance may be obtained, enabling corroborative tests to be at once applied. If, however, no satisfactory evidence is obtained from the preliminary tests, it is determined whether the substance contains nitrogen, sulphur, halogens or phosphorus, a more complete classification for the purposes of identification being based on the elements present.

Before commencing the analysis it should be ascertained, for example by treatment with solvents, whether the sample is one

compound or a mixture, and if the latter a separation by chemical or physical means should be effected. No general rule for isolation of the constituents can be given, but fractional distillation, crystallisation and solution methods are usually used, and extraction from an acid or alkaline aqueous solution with an immiscible solvent is often helpful when one component has basic or acidic properties.

PRELIMINARY TESTS

I. The Action of Heat

A small quantity of the substance is heated on a piece of foil or on the back of a penknife and the odour, behaviour, and presence of any inorganic residue is noted.

OBSERVATIONS	COMPOUNDS
ODOUR on heating:	Given by:—
(i) Very objectionable	Acriflavine, Benzocaine, Carbromal, Phenocol, Physostigmine, Yohimbine.
(ii) Garlic-like ...	Arsamin, Chloralamide, Disodium Methylarsenate, Neoarsphenamine, Sod. Cacodylate, Sulphonal, Thiosinamine.
(iii) "Burning sugar" ...	Citrates, Lactates, Tartrates, Sugars, Calcium Saccharate, Picrotoxin, Strophanthin, Glycerophosphates (very slight odour).
(iv) Resembling pyridine (or "burnt feathers")	The Purine Bases, Caffeine, etc., and their compounds.
(v) Phenolic ...	Amidopyrine, Apomorphine, Morphine, Cinchona alkaloids, Malachite Green, Phenazone, Amylocaine Hydrochloride, Strychnine.
	Inorganic Benzoates, Salicylates and Phenol sulphonates, Phenol compounds.
	Dimol, Potassium Hydroxyquinoline Sulphate, Tribromophenol.
	The characteristic odour of Salicylic Acid on heating is obtained with all its organic derivatives.
(vi) Aromatic ...	Aconitine, Atropine, Cinchophen, Cocaine, Colchicine, Hyoscine, Papaverine, Sod. Cinchonamate, Sod. Hippurate.
(vii) "Sweetish" odour ...	Allantoin, Picrotoxin, Resorcin, Saccharin, Ethylmorphine.
(viii) "Alcoholic" ...	Chlorbutol, Homatropine, Soluble Barbitone, Urethane.
(ix) Amine odour ...	Amydracaine Hydrochloride, Amylocaine Hydrochloride, Apomorphine, Betaine, Colchicine, Cryogenine, Ethylmorphine, Hexamine, Papaverine, Pilocarpine, Piperazine, Sodium Hippurate, Urea, Emetine Hydrochloride (resembling haddock).
(x) Odour of burning animal or nitrogenous matter	Albumin Tannate, Bile Salts, Dimol, Nuclein, Silver Proteinates, Eurobin.
(xi) Pleasant odour ...	Sparteine Sulph. (pea-like). Atropine (nasturtium-like).

OBSERVATIONS	COMPOUNDS
APPEARANCE on heating:	
(i) Low-melting solids (below 100°)	Acetophenone, Oxalic Acid, Stearic Acid, Benzocaine, Betol, Bromal Hydrate, Chloral Hydrate, Chlorbutol, Cocaine, Colchicine Salicyl., Coumarin, Guaiacol Benz. and Carb., Homatropine, Phenazone Salicylate, Physostigmine, Piperazine Tartrate, Salacetol, Salol, Thiosinamine, Thymol, Tribromophenol, Urethane.
(ii) Coloured fumes (a) of Iodine (b) Yellowish-brown	Alkaloidal Periodides, Emet. Bism. Iodide, Iodoform, Thymol Iodide, Tetraiodopyrrol. Acriflavine, Chysarobin, Colchicine, Eurobin, Fluorescein.
(iii) Incandescent residue	From Calcium and Magnesium Salts.
(iv) Yellow sparks	Gallic Acid, Alum. Aceto-tart., Zinc Sulphocarb., Urea.
(v) Boils and volatilises without appreciable charring.	Acetylsalicylic, Malic, Oxalic and Succinic Acids. Chloralamide, Cryogenine, Holocain, Naphthalene Tetrachloride, Phenazone, Piperazine, Propional, Urea.

If an **inorganic residue** is obtained on ignition the substance is probably the metallic salt of an organic acid or phenol, and the following compounds, classified according to the metal present, are frequently employed therapeutically. In most cases tests for the acidic radicle, which can usually be separated as the sodium salt by treatment of the substance with alkali, are described later.

THE METAL PRESENT IN RESIDUE AFTER IGNITION	COMPOUNDS TO BE EXAMINED FOR:—
Aluminium ...	Aceto-tartrate.
Antimony (with Sodium) ... (with Potassium) ...	Sodium Antimonyltartrate. Potassium Antimonyltartrate.
Bismuth (with Sodium or Potassium or both)	The Alkali Bismuthyl Tartrates. Benzoate, Citrate, Gallate, Oxyiodogallate, Naphthol, Tribromophenol, Salicylate, etc.
Calcium ...	Acetylsalicylate, Formate, Lactate, Glycerophosphate, Saccharate, Guaiacolsulphonate. N.B.—Calcium and Sodium are found in the residues from extracts and naturally occurring substances.
Iron ...	Ammon. Citrate, Tartrate, Oxalate, etc. Glycerophosphate, Peptonate, Valerianate.
Magnesium ...	Acetylsalicylate, Borocit., Glycerophosphate, Ricinoleate.
Manganese ...	Butyrate, Glycerophosphate.
Potassium ...	Acetate, Oxalate, Borotart., Citrate, Formate, etc.
Silver ...	Colloidal. Proteinates, Nucleinate, etc.
Sodium ...	Indigo Carmine. Soluble Barbitone, Mercurochrome, Neosphenamine, Acetate, Formate, Glycerophosphate, Salicylate, etc.
Zinc ...	Bile Salts. Oleate, Phenolsulphonate, Valerianate. N.B.—Zinc salts are obtained on igniting some commercial dyes, e.g., Methylene Blue, Malachite Green.

2. The action of Concentrated Sulphuric Acid

About 0.2 g. of the substance is treated with 1 ml. of sulphuric acid at first cold and then with heating.

OBSERVATIONS	COMPOUNDS
Cold Sulphuric Acid:—	
<i>Insoluble</i>	Saturated and aromatic hydrocarbons and their halogen derivatives:—Benzene, Xylol, etc.
<i>Effervescence—</i>	
(i) HCl, HBr, HI ..	From salts with organic bases, e.g.:— Alkaloidal Hydrochlorides, Acriflavine, Betaine Hydrochloride, Procaine Hydrochloride, etc.
(ii) Chlorine	Chloramine and Dichloramine-T.
<i>Odour of Sulphur Dioxide</i>	Neoarsphenamine.
<i>Coloration—</i>	
(i) Deep red ..	With certain glycosides, e.g.:— Salicin, Amygdalin, Arbutin. Aloes, Acriflavine, Iodised Oils, Proflavine, Phenolphthalein, Santalol.
(ii) Light red ..	Nicotine, Physostigmine.
(iii) Green	Methylene Blue.
(iv) Blue	Strophanthin (changes to brown). Amyl Nitrite (changes to brown).
Hot Sulphuric Acid:—	
<i>Effervescence—</i>	
(i) Without charring	Formic Acid, Oxalic Acid, Betaine Hydrochloride, Urea.
(ii) With blackening	Carbohydrates, some glycosides, Hydroxy-acids such as Citric, Tartaric, Lactic. Apiol, Malachite Green.
<i>Iodine evolved</i>	Ethyl Iodide, Bismuth Oxyiodogallate, Emetine Bismuth Iodide, Thymol Iodide, Tetraiodopyrrol.
<i>Pungent Vapours—</i>	
Without effervescence and blackening ..	Acetic, Benzoic, Salicylic, Succinic, Acetylsalicylic Acids, Phenols and metallic derivatives. Brometone, Chlorbutol, Chloral Hydrate.
<i>No blackening</i>	Benzoic, Salicylic, Acetylsalicylic, Meconic Acids and many of their compounds; Phenol. Allantoin (red soln.), Alloxan (yellow soln.), Amidopyrine, Amydracaine Hydrochloride, Chloralamide (chloral odour), Ethyl Bromide Fluorescein, Purine Bases.

3. The action of Alkali.

Test solubility of substance in water, then add strong caustic soda solution and warm.

OBSERVATIONS	COMPOUNDS
Soluble in water ..	The following classes of common compounds are soluble:— Lower members of Monohydric, and also Di- and Trihydric Phenols. Lower members of Aliphatic Alcohols, Acids, Amines, Amides, Amino-Acids, Aldehydes, Acetone. Glycosides are fairly soluble. Carbohydrates, except Starch and Cellulose. Salts of organic acids or bases.
Caustic Soda with Heating:—	
<i>Substance dissolves</i> ..	Acids, Amides, Phenols, some Esters.
<i>Precipitate forms</i> ..	This may be hydroxide from metallic salt (which would be detected in Test 1). Organic Base from Salts (Morphine dissolves in excess KOH).
<i>Odour of Ammonia</i> ..	From Ammonium Salts, Amides, Ureides, Urea compounds, Chloralamide.
<i>Odour of Amine</i> ..	From salts, e.g., Aniline Hydrochloride, Acetanilide, Exalgin.
Coloration—	
(i) Deep red.. ..	Phenolphthalein.
(ii) Yellow cold turning red on warming	Many sugars.
<i>Fluorescence</i>	Fluorescein, Eosin.

Reaction for Alkaloids

The solution should be tested for alkaloids by means of the usual reagents such as Mayer's reagent, gold chloride or picric acid. The table below may be useful in the identification of a common alkaloid.

In addition to the synthetic Cocaine substitutes the following bodies react in some cases like alkaloids:—

Bromethylformine, Amidopyrine, Phenazone, Phenocoll, Piperazine, Piperidine, Potassium Hydroxyquinoline Sulphate, Pyridine, Quinoline, Thiosinamine, and some dyes such as Acriflavine.

The purine bases, Caffeine, Theobromine, Theophylline, do not respond to any of the usual tests.

Reaction with Fehling's Solution

It should be determined whether the substance reduces Fehling's before and after hydrolysis with dilute acid.

Substances readily reducing Fehling's Solution before hydrolysis.	Monosaccharides: Dextrose, Lævulose, Mannose, etc. Disaccharides: Lactose, Maltose, etc. Fehling's is also reduced by some aldehydes, e.g., Chloral, and polyhydric phenols, e.g., Resorcin, Pyrogalllic Acid, and by Amylocaine Hydrochloride, Camphoric Acid, Chloroform, Chloralamide, Creatinine, Cryogenine.
Substances readily reducing Fehling's Solution only after hydrolysis.	Disaccharides: Sucrose. Glycosides: Aesculin, Salicin, etc.

If sufficient data for identification have not been obtained from the above tests the compound should be examined for nitrogen, sulphur, halogens and phosphorus. Lassaigne's method is usually satisfactory, and consists in adding about 0.1 g. of the substance to a small piece of clean molten sodium in a test tube, and, after thorough heating, the mass is carefully treated with water and filtered.

Nitrogen

A portion of the above solution is tested for cyanide by heating with ferric sulphate, making acid with hydrochloric acid and adding 1 drop of ferric chloride solution. A blue solution or precipitate of Prussian blue indicates presence of nitrogen in the substance. Cyanamide, given by urea and derivatives, should also be tested for by means of silver nitrate, the silver salt being soluble in nitric acid but insoluble in ammonia. Sodium sulphocyanide may be formed if the substance contains nitrogen and sulphur.

Sulphur

The formation of a deep violet colour on adding a small crystal of sodium nitroprusside to some of the solution from the sodium ignition indicates presence of sulphur. The solution may also be tested for sulphide by means of lead acetate.

Halogens

These are identified in the usual way, after removal of hydrocyanic acid if necessary, by boiling some of the above solution with nitric acid.

Phosphorus

This element can be detected as phosphate after ignition of the substance with potassium carbonate and potassium nitrate.

It is now possible to decide to which of the following groups the unknown compound belongs:—

- GROUP I.** *Organic compounds not containing halogens, nitrogen, sulphur or phosphorus,—see below.*
- GROUP II.** *Compounds containing halogens* (and free from phosphorus, sulphur or nitrogen), page 235.
- GROUP III.** *Compounds containing nitrogen* (and free from halogens, sulphur and phosphorus), page 235.
- GROUP IV.** *Compounds containing sulphur* (and free from halogens, nitrogen and phosphorus), page 238.
- GROUP V.** *Compounds containing nitrogen and sulphur* (and free from halogens and phosphorus), page 238.
- GROUP VI.** *Compounds containing nitrogen and halogens* (and free from sulphur and phosphorus), page 238.
- GROUP VII.** *Compounds containing halogens, nitrogen and sulphur* (phosphorus absent), page 238.
- GROUP VIII.** *Compounds containing phosphorus*, page 238.

The distinguishing tests in each group, which should be carried out in the order given, together with a knowledge of the physical properties of the substance, should enable it to be identified with the aid of the special tests in the Corroborative Chart. When the groups contain a large number of compounds they are divided, as far as possible, according to their chemical type, which should enable any uncommon medicinal body, not mentioned in the scheme, to be classified.

GROUP I. Organic Compounds not containing Halogens, Nitrogen, Sulphur or Phosphorus.

I. Acids

By treatment with sodium carbonate or by an approximate titration, using N/1 sodium hydroxide and phenolphthalein, it should be determined whether the substance is an acid. A neutral solution of the sodium salt is then tested with ferric chloride and calcium chloride, the behaviour of some common acids being shown in the following table. The polyhydric phenols, such as pyrogallol, and also a few acids containing nitrogen, although not belonging to this group, are also included for convenience.

Table of The Common Acids

REAGENT	OBSERVATIONS	ACIDS
Ferric Chloride.	<i>Purple Coloration.</i> (i) Not discharged by acetic acid.	Salicylic Acid. Acetyl-salicylic Acid also gives this on warming with the reagent.
	(ii) Discharged by acetic acid.	Carbolic Acid.
	<i>Red Coloration.</i> (i) Discharged by HCl to yellow colour.	Formic and Acetic Acids.
	(ii) Not discharged by HCl but by HgCl ₂ .	Sulphocyanic Acid.
	(iii) Not discharged by HCl or HgCl ₂ .	Meconic Acid.
	(iv) Blackened by excess of KOH solution.	Pyrogalllic Acid.
	<i>Coloured Precipitate.</i> (i) Buff coloured. The addition of HCl gives white crystalline body.	Benzoic, Hippuric and Cinnamic Acids.
	(ii) Reddish-brown ppt. (a) Giving clear solution with HCl. (b) White crystals with HCl.	Succinic and Phthalic Acids. Uric Acid.
	(iii) Blue - black, giving brown solution with H ₂ SO ₄ .	Gallic and Tannic Acids.
	(iv) Prussian blue, discharged by NaOH. (v) Brown solution giving Prussian blue on adding SO ₂ .	Ferrocyanic Acid. Ferricyanic Acid.
Calcium Chloride to cold solution.	(i) White precipitate soluble on boiling.	Malonic Acid.
	(ii) White ppt. soluble in HCl but insoluble in acetic acid.	Oxalic Acid.
	(ii) Crystalline powder soluble in HCl and acetic acid.	Tartaric, Fumaric Acids.
Calcium Chloride on boiling.	(i) White ppt. on adding 1 drop ammonia solution, and soluble in acetic acid.	Citric Acid.
	(ii) White ppt. on adding equal volume of alcohol. Soluble in acetic acid.	Malic Acid.
	(iii) Greyish-white ppt. Soluble in HCl to pinkish solution.	Tannic and Gallic Acids.

Other acids which should be tested for are Agaric, Cacodylic, Camphoric, Cholic, Coumaric. Valerianic, Oleic and Stearic acids have a characteristic colour or appearance.

2. *Phenols and Lactones*

The presence of these compounds is indicated by solubility in sodium hydroxide solution but not in sodium carbonate.

PHENOLS.—Phenol, Thymol, α - and β -Naphthol, Dimol (contains also some nitrogenous matter).

LACTONES, dissolving slowly in hot alkali and reprecipitated by acid. Coumarin (has characteristic odour and gives yellow solution with caustic alkali), Santonin.

3. *Aldehydes and Ketones*

Aldehydes reduce ammoniacal silver nitrate and give colour with Schiff's reagent. Ketones and aldehydes form derivatives with phenylhydrazine and semicarbazide, the melting-points of which are useful for identification, and many give crystalline compounds with sodium bisulphite.

The following should be tested for:—Acetaldehyde, Formaldehyde, Paraformaldehyde, Benzaldehyde, Acetone, Acetophenone.

4. *Esters*

These compounds, when hydrolysed by alkali, yield an acid and an alcohol or phenol.

- (i) Esters derived from alcohols usually have a pleasant odour.

Ethyl Acetate, Amyl Valerianate, Methyl Salicylate, Benzyl Benzoate, and Succinate.

- (ii) Esters derived from phenols and used therapeutically are often compounds of either Salicylic Acid or Guaiacol.

Salacetol, Salicyl Salicylate, Salol, Guaiacol Benzoate, Cinnamyl Salicylate, Camphorate, Salicylate, Valerianate.

5. *Hydrocarbons*

These are insoluble in cold sulphuric acid; aromatic compounds have a characteristic odour, and must be identified by physical properties.

Benzene, Light Petroleum, Toluene, Xylene, Paraffin.

6. *Mercury Compounds*

The substance should be tested for mercury after destroying organic matter with concentrated sulphuric and nitric acids.

Common compounds are the Benzoate, Carbolate, Lactate, Oleate, Phenyl Salicylate, Succinate, Succinimide; Mercurochrome, Flumerin.

7. *Compounds Soluble in Water.*

CARBOHYDRATES (except Starch and Cellulose) *Aliphatic Alcohols*, *Glycosides* (moderately soluble), *Polyhydric Phenols*.

- (i) *Sugars and Glycosides.*

These would have been indicated by Preliminary Test 5. Glycosides likely to be present are:—Aesculin, Digitalin, Digitoxin (not very soluble in water), Salicin, Phloridzin, Strophanthin.

- (ii) *Common Alcohols.*

Methyl, Ethyl, Propyl and Isopropyl, Amylene Hydrate (camphoraceous odour).

- (iii) *Polyhydric Phenols.*

Resorcinol, Pyrogallol.

8. Substances having Characteristic Physical Properties

The following members of this group can be recognised by properties such as odour and appearance.

LIQUIDS		SOLIDS	
SUBSTANCE	DISTINGUISHING PROPERTY	SUBSTANCE	DISTINGUISHING PROPERTY
Apiol (may, however, be crystalline)	Green liquid. Peculiar odour.	Aloes, Aloin	Yellowish-brown with characteristic odour.
Amyl Alcohol	Characteristic odour.	Coumarin	Fragrant odour. Sublimes at 100°.
Capsicin	Reddish-brown oily mass.	Podophyllin	Characteristic odour.
Resorcinol Mono-acetate	Oily substance with slight acetic acid odour.	Acetophenone	Odour resembling almonds and jasmine.
Santalol	Characteristic odour.	Terpin Hydrate	Slightly aromatic odour. Sublimes at 100°.

Test specially for the neutral compounds Podophyllotoxin, Cantharidin, Elaterin. Also for Anthrarobin.

GROUP II. Compounds containing Halogens. (Nitrogen, Sulphur and Phosphorus being absent.)

The following are commonly occurring substances:—

CHLORINE COMPOUNDS.

Amylene Chloral, Butylchloral, Ethyl Chloride, Carbon Tetrachloride, Chlorbutol, Chloral Hydrate, Chloroform, Naphthalene Tetrachloride.

BROMINE COMPOUNDS.

Bromal Hydrate, Brometone, Bromoform, Camphor Monobromide Ethyl Bromide, Tribromophenol and Bismuth Salt.

IODINE COMPOUNDS.

Ethyl Iodide, Thymol Iodide.
Iodised oils.

GROUP III. Compounds containing Nitrogen. (Halogens, Sulphur and Phosphorus being absent.)**1. The Alkaloids**

Members of this class of compounds, including some synthetic cocaine substitutes, would be indicated by Preliminary Test 4.

In the following table most of the substances in general use are arranged according to their behaviour with certain reagents, and by testing with these in the order named it is possible to determine rapidly in which group an unknown alkaloid occurs, when it is identified by physical properties and special reactions.

In each test about 2 ml. of a 1% solution of the alkaloidal salt, or saturated if less soluble, and a few drops of the reagent are used, an immediate precipitate only being noted. Before adding potassium ferrocyanide 5%, platinum chloride 5%, potassium chromate 5%, or picric acid, the solution is slightly acidified with dilute hydrochloric acid. Perchloric acid and N/10 potassium permanganate are added to the neutral solution.

It must be remembered that this scheme is intended only as a guide, and results must not be interpreted too rigidly, since uncommon alkaloids are not included, and also anomalous results might possibly occur with impure alkaloids or with any deviation from the above conditions.

REAGENT	ALKALOIDS which give a distinct precipitate with the reagent	Other Alkaloids which give a distinct ppt., but which would be detected in previous groups
I. Potassium Ferrocyanide in slightly acid solution.	Apomorphine Emetine Berberine Papaverine Cinchonidine Quinidine Cinchonine Strychnine (Yohimbine if impure).	
II. Perchloric Acid to neutral solution.	(i) <i>Immed. reducing</i> $KMnO_4$ Aconitine Hydrastine Veratrine (ii) <i>Not reducing</i> $KMnO_4$ <i>immed.</i> Cocaine Ergotinine Holocain	Berberine. Emetine. Papaverine. Strychnine.
III. Platinic Chloride in slightly acid solution.	Diamorphine Nicotine Quinine	Apomorphine. Berberine. Cinchonidine. Cinchonine. Emetine. Hydrastine. Holocain. Papaverine. Quinidine. Strychnine.
IV. Potassium Chromate in slightly acid solution.	Yohimbine (If impure, yohimbine may precipitate in the potassium ferrocyanide group)	All the alkaloids previously mentioned give ppt. except Aconitine, Ergotinine and Nicotine.
V. Picric Acid in slightly acid solution.	(i) <i>Immed. reducing</i> $KMnO_4$ Codeine Morphine Ethylmorphine Narceine Gelsemine Eserine (ii) <i>Not reducing</i> $KMnO_4$ <i>immed.</i> Amydracaine Hyoscyamine Atropine Procaine Benzamine Sparteine Homatropine Stovaine Hyoscine	All the alkaloids previously mentioned give a ppt. with this reagent.
VI. Mayer's and Gold Chloride.	Coniine Pilocarpine	All the alkaloids in this table give ppt.

COLOUR REACTIONS WITH FROEHDE'S REAGENT

A few drops of the reagent are added to a little of the dry alkaloid in a white dish, the colour being observed after a few minutes. Colorations, being due to reduction of the reagent, are also given by some non-alkaloidal substances e.g., Salicin, Phloridzin, Colocynthin.

The following alkaloids give a distinct colour:—

Apomorphine (bluish-green)	Morphine (deep red).
Berberine (dark greenish-brown).	Narceine (reddish-green).
Codeine (bluish-green).	Nicotine (red).
Diamorphine (red).	Papaverine (bluish-green).
Emetine (green).	Quinidine (pale green).
Ethylmorphine (yellow, turning green).	Quinine (pale green).
Hydrastine (green).	Veratrine (red).
	Yohimbine (violet).

The following also behave in some respects like alkaloids:—Amidopyrine, ridine, Phenazone, Phenocoll, Piperazine, Piperidine, Quinoline.

Ferro- and ferricyanides used to differentiate numerous alkaloids microscopically.—W. M. Cumming and D. G. Brown, *Pharm. J.*, ii/1925, 141.

Purine Bases

These are weak bases reacting with only a few alkaloidal reagents, and are characterised by giving the murexide test, see Caffeine, p. 257.

Caffeine, Theophylline, Theobromine and also their compounds with sodium its such as Theobromine Sodium Salicylate. Uric Acid.

Urea Compounds and Ureides

Ureides are hydrolysed by strong potassium hydroxide, slowly in some cases, to the potassium salt of the acid and urea, the latter compound undergoing further decomposition giving potassium carbonate and evolving ammonia.

N.B.—Amides, e.g., Acetamide and Chloralamide, also yield ammonia on heating with alkali solution, but without formation of carbonate.) Note also precipitation with Millon's reagent, *v.* Barbitone, p. 253.

Test for Urea and Urethane (both readily soluble in water) and the ureides Iloxan, Allantoin, Allobarbitone (Dial), Barbitone, Phenobarbitone, Propional, Moneryl, Veronal, etc.

Amines

Test for primary amines by the carbylamine reaction. Warm the substance with alkali and a little chloroform, and note any isocyanide odour.

This reaction is not given by primary amines capable of forming non-volatile salts, e.g., Aminophenols, Aminocarboxylic Acids, Aminosulphonic Acids.

If however, after heating, a sample is withdrawn on a glass rod and held in the current of air breathed out from the nose, the carbon dioxide combines with the alkali and liberates the volatile carbylamine derivative, the odour of which soon becomes noticeable.—*J. chem. Soc. Abstr.*, ii/1924, 430.

(i) Aliphatic Primary Amines

After solution of the substance in excess HCl and treatment with sodium nitrite these compounds yield an alcohol on heating, but they are rarely met with except as the amino-acids. Asparagine, for example, is converted into malic acid by nitrous acid.

(ii) Aromatic Primary Amines

These bodies form a diazonium compound with sodium nitrite and acid, which usually couples with an alkaline solution of β -naphthol forming dyes, and also gives a phenol on heating. Examine for Aniline, Benzocaine, Phenocoll, Sodium Aminarsonate.

The following give reactions for a primary amine after hydrolysis:—

Acetanilide, Acetyl-*p*-amidosalol, Phenalgin, Phenacetin.

(iii) Secondary Amines

Treatment with nitrous acid forms a nitroso compound which can be identified by Liebermann's reaction.

Methylacetanilide gives the secondary amine, methylaniline, after hydrolysis.

The following compounds give colours with nitrous acid:—

Adrenaline	red colour.	Orthocaine	yellow colour
Amidopyrine	violet colour.	Phenazone	green colour.

Inorganic Matter Present

Important compounds are those of Silver, e.g., Silver Proteinates, Colloidal Silver. The presence of inorganic matter in compounds of this group may note a metallic cyanide, ferro- or ferricyanide.

Mercury Cyanide and Oxycyanide.

Amino-Acids

These are neutral compounds usually soluble in water and insoluble in alcohol and ether.

Common substances are:—

Pyruvic Acid.

Hydrolysed by HCl to benzoic acid and glycocoll.

Glycocoll.

Gives deep blue colour with CuSO_4 due to copper glycocoll. FeCl_3 gives intense red colour discharged by acids.

Anthranilic Acid.

Heated with calcium oxide yields aniline. Treatment with nitrous acid and warming gives salicylic acid.

Betaine

Usually occurs as the hydrochloride which gives a very acid solution in water. Fusion with KOH gives trimethylamine.

Forms a periodide on adding a solution of iodine.

7. Esters of Nitrous and Nitric Acids

Amyl and Ethyl Nitrites have characteristic effect on inhaling. (See Vol. I, p. 148)

Glyceryl Trinitrate, Mannityl Hexanitate, and Erythrityl Tetranitate are readily hydrolysed giving a nitrate. Being very explosive they usually occur only in solution or massed with an inert substance.

8. Nitro-compounds

Reduction in acid solution gives primary amines which can be identified as described above. Usually poisonous and not used medicinally.

GROUP IV. Compounds containing Sulphur. (Halogens, Nitrogen and Phosphorus being absent).

Phenolsulphonates of Zinc and Sodium, Sulphorcinates, Sulphonal, Thioresorcin.

GROUP V. Compounds containing Nitrogen and Sulphur (and free from Halogens and Phosphorus).

A solution of the substance should be tested for sulphate, and if present the organic base, which is probably alkaloidal, should be examined as described in Group III, p. 235.

Other substances are:—Albumin Tannate, Bile Acids and Salts, Glycogen, Indigo Carmine, Neoarsphenamine, Potassium Hydroxyquinoline Sulphate, Proflavine, Saccharin, Silver Proteinates, Thiosinamine.

GROUP VI. Compounds containing Nitrogen and Halogens (and free from Sulphur and Phosphorus).

A solution should be tested for ionised halogen by means of silver nitrate which indicates the presence of a salt of an organic base. The latter if alkaloidal is described in Group III, p. 235.

CHLORINE COMPOUNDS.

Acriflavine, Arsphenamine, Betaine Hydrochloride (*v.* above), Chloralamid, Chloramine—T, Dichloramine—T, Fuchsine, Malachite Green.

Cocaine Substitutes, e.g., Amydracaine, Amylocaine, Procaine, etc., are mentioned in Group III, p. 235.

BROMINE COMPOUNDS

Adalin, Bromethylformine, Bromo-valerianyl-urea, Dibromo-tannin-gelatin.

IODINE COMPOUNDS

Tetraiodopyrrol.

GROUP VII. Compounds containing Halogens, Nitrogen and Sulphur (Phosphorus absent).

Methylene Blue, Thiosinamine Ethyl Iodide.

GROUP VIII. Compounds containing Phosphorus.

Acid Glycerophosphoric and Salts.

Nuclein, Nucleinic Acid, Lecithin.

CORROBORATIVE TESTS

The following chart gives the physical constants and characteristic reactions of many medicinal compounds. It will be found useful in confirming results obtained by the preceding method of analysis. The data obtained with the tests with alkaloidal reagents are of special interest in dealing with the *Purine Bases*, which in general do not precipitate, or with some non-alkaloidal substances, for example, *phenazone*, which behave like alkaloids.

In trying the effect of heat about 0.1 g. in a 3 by $\frac{1}{2}$ in. test-tube should be used. For the Bromine Water Test, Mayer's Test, Gold Chloride Test, Picric Acid Test and Dragendorff's Test, the 1 in 25 solution of the substance is used, if not soluble to that extent, a saturated solution is employed. For formulæ for preparation of Mayer's, and Dragendorff's Solution, *vide* p. 24 and 62, Gold Chloride solution is used 1 in 20.

Other alkaloidal reagents are the following:—

AMMONIUM SULPHOMOLYBDATE. Froehde's Reagent. Ammonium molybdate, g., in concentrated sulphuric acid, 100 ml.

ERDMANN'S REAGENT. Mix 6 drops of nitric acid (sp. gr., 1.25) with water, 100 ml., add 10 drops of this to 20 ml. of concentrated sulphuric acid.

MANDELIN'S REAGENT. Sulphovanadic acid. A 1% solution of sodium vanadate in concentrated sulphuric acid.

MERCURIC CHLORIDE SOLUTION. 1 in 20.

PLATINIC CHLORIDE. 1 in 20.

PHOSPHOTUNGSTIC ACID. Dissolve sodium tungstate, 100 g., and sodium phosphate, 70 g., in water, 500 ml., and acidify with nitric acid.

PHOSPHOMOLYBDIC ACID. Sonnenschein's Reagent. Consists of a solution of sodium phosphomolybdate in nitric acid, prepared by acidifying a warm solution (50° to 60°) of sodium phosphate with nitric acid, and adding an excess of ammonium molybdate solution. The yellow precipitate is separated, washed with water, then with nitric acid and dissolved in a hot solution of sodium carbonate (using as little as possible). The solution is evaporated to dryness and ignited at low red heat till all ammonium salts are volatilised, the residue moistened with nitric acid and again ignited. The product, consisting of sodium phosphomolybdate, is dissolved in ten times its weight of water, and nitric acid (sp. gr., 1.42) added until the precipitate at first produced redissolves.

TANNIC ACID. A solution of tannic acid, 1 g., in water, 8 ml., and alcohol, 1 ml.

WAGNER'S REAGENT. Iodine in potassium iodide. Iodine, 5 g.; potassium iodide, 10 g.; water, 100 ml.

In using this reagent, e.g., in testing for complete extraction in alkaloidal assays, it should be noted that water saturated with ether and then acidified gives a precipitate of iodine on adding this reagent. The precipitate may be distinguished from that due to an alkaloid by adding water. If due to iodine, it will redissolve.

Contractions used in the chart are as follows:—

a.	= after.	misc.	= miscible.
ac.	= acid.	mod.	= moderate.
alc.	= alcohol(ic).	od.	= odour.
alk.	= alkaline.	or.	= orange.
arom.	= aromatic.	ppt.	= precipitate.
b.	= before.	pt.	= partially.
bl.	= blue.	quick.	= quickly.
blk.	= black.	react.	= reactions.
brns.	= burns.	res.	= residue.
br.	= brown.	rediss.	= redissolves.
c.	= with.	sat.	= saturated.
ch.	= chars.	sl.	= slight, slightly.
col.	= colour.	s.	= without.
crm.	= cream.	slow.	= slowly.
dec'm.	= decomposes.	sns.	= softens.
dk.	= dark.	sol.	= solution.
dist.	= distillate.	str.	= strongly.
Drag.	= Dragendorff.	sub.	= sublime or sublimate.
eff.	= effervescence.	v.	= very.
gr.	= green.	vap.	= vapour.
inf.	= inflammable.	vi.	= violet.
insol.	= insoluble.	wh.	= white.
m.	= melt(s).	yell.	= yellow.

Analar (British Drug Houses Ltd. and Hopkin & Williams Ltd.) is a brand of chemicals for analytical purposes. Chemicals of reagent purity are also obtainable under the names *Judex* (The General Chemical and Pharmaceutical Co., Ltd.) and *Sterling* (Thomas Tyrer & Co., Ltd.).

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in-)	SOL. ALC. (1 in-)	MAY- ER'S.	GOLD CHL.	ACID PIC- RIC.	DRA
1	Acetanilide	M., sub., vap. burns.	113 -115	210	4 $\frac{1}{4}$	Nil	Nil	Nil	Br. ppt.
2	Acetannin	M., ch., br. vap. c. acetic od.	—	V. sl.	V. sl.	Nil	Nil	Nil	Nil
3	Acetone	Evap. c. inflam. vap.	—	Misc.	Misc.	Nil	Nil	Nil	Nil
4	Acetophen- one	Evaps., does not ch.	18	V. sl.	Misc.	Nil	Nil	Nil	Br. ppt.
5	Acetyl-<i>p</i>- amidosalol	M., turns yell., and ch., vap.	180 -185	V. sl.	Sl.	Nil	Nil	Nil	Nil
6	Acid Acetyl- salicylic	M.c. acetic od., ch. vap.	135 -138	400	5	Nil	Nil	Nil	Nil
7	Acid Agaric	M.c. eff., ch., br. dist. and inf. vap.	About 140°	Insol.	V. sl.	Nil	Nil	Nil	Nil
8	Acid Benzoic	M., sub., brns. c. irrit. od.	121 -122	450	3	Nil	Nil	Nil	Nil
9	Acid Cacodylic	M., ch. Garlic vap. As flame.	About 200	$\frac{1}{2}$	4	Nil	Nil	Nil	Nil
10	Acid Camphoric	M., sub. c. inf. vap.	185 -187	About 160	About 1 $\frac{1}{2}$	Nil	Nil	Nil	Nil
11	Acid Cholalic (Colalin)	Part. m., Ch. c. alk. inf. vap.	—	Sl.	About 1	Nil	Nil	Nil	V. s red. br. ppt.

O.	BROM. AQ.	SPECIAL TESTS.
1	Wh. ppt.	Hydrolysed by HCl or KOH sol. to aniline and acetic acid. 0·1 g. boiled with HCl, 2 ml., then mixed with 3 ml. of phenol solution (1 in 20) and 5 ml. of sat. chlorinated lime sol., turns br.-red changing to blue on adding AmOH (Indophenol Test, U.S.P.). Heated with boric acid over a naked flame, gives yell. residue and sweet od. Phenacetin gives yell., phenazone a pink, and naphthalene an orange. 0·001 g. in 5 ml. wtr. heated with NaOH and few drops chloroform gives phenyl isocyanide od.
2	Nil	Shaking c. ethyl alcohol and sulphuric acid gives od. of ethyl acetate.
3	Nil	Oxidation c. $K_2Cr_2O_7$ and H_2SO_4 gives acetic and formic acids. Combines c. chloroform in presence of caustic alkali to form acetone-chloroform (colourless crystals, m.p. 96° , insol. in water). In aq. sol. can be thrown out by salts, e.g., calcium chloride. Iodoform Test see <i>Urine Examination</i> . 0·00001 ml. in 10 ml. wtr. warmed to 70° . 1 g. KOH and 10 drops salicylaldehyde gives a purplish-red ring.
4	Sl. ppt. rediss.	0·01 g. in 5 ml. wtr. with hydroxylamine hydrochlor. forms acetoxime, $C_6H_5C(N\cdot OH)\cdot CH_3$ (white ppt., m.p. 59°). This by boiling c. dil. H_2SO_4 in glacial acetic acid is converted into acetanilide (Beckmann's reaction), and then aniline (od.) and acetic acid.
5	Nil	Yields salicylic acid on hydrolysis c. NaOH. Is not hydrolysed by HCl. Does not give Isonitrile Test, but on adding the chloroform it gives a br.-red. When hydrolysing with dilute NaOH it turns blue, changing to reddish-violet on boiling; the blue reappearing on cooling is changed to red with HCl.
6	No ppt.	0·0001 g. in 5 ml. wtr. boiled 2 mins. c. HCl a few drops, neutralised c. NaOH and one drop $FeCl_3$ added—purple.
7	Nil	Turns gelatinous and soapy on boiling c. wtr. 0·00001 g. in 5 ml. wtr. with 15 ml. H_2SO_4 cooled and a few drops syrup added—purple in a few minutes.
8	Nil	0·001 g. in 0·5 ml. wtr. gives light buff ppt. c. 1 drop $FeCl_3$. Further 0·001 g. warmed sl. c. 3 drops 25% formic acid and the sol. neutralised c. lime water and evaptd. to dryness; residue heated in sm. tube gives benzaldehyde od. Lime water does not ppt. the aq. sol. either hot or cold. Lead acetate does not either, but it ppts. benzoates.
9	Nil	0·005 g. in 5 ml. wtr. and a few drops hypophosphorous acid—cacodyle odour in a few seconds.
0	Nil	Gives sublimate of anhydride, m.p. $21\cdot7^\circ$, on heating.
1	V. sl. ppt.	Gives blue unstable compounds with iodine resembling starch iodide. 0·0001 g. in 5 ml. water responds as Ac. Agaric. c. H_2SO_4 and syrup.

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in-)	SOL. ALC. (1 in-)	MAY- ER'S	GOLD CHL.	ACID PIC- RIC.	DRAG
12	Acid Cinnamic	M., wh. sub. and inf. vap	132 -135	Sl.	10½	Nil	Nil	Nil	Nil
13	Acid Citric	M., ch., c. inf. vap.	Bec. anhyd. at 135 then M. at 153.	0·6	1½	Min- ute crys- tals on stand- ing.	Nil	Nil	Nil
14	Acid Coumaric	M., ch. c. inf. vap.	200	600	12 (or less).	Nil	Nil	Nil	Nil
15	Acid Cresylic	Evaps. vap. brns.	—	70	Misc.	Nil	Bl. ppt. grad. forms	Nil	V. sl. ppt.
16	Acid Gallic	Part m. and ch., or. sub. and br. vap. brns.	—	100 (ap- prox.)	5	Nil	Dir- ty br. ppt.	Nil	Nil
17	Acid Glycero- phosph.	Evaps. Res. effs. and ch., vap. brns.	—	Misc.	Misc.	Nil	Nil	Nil	Nil
18	Acid Hippuric	M. to clear liq., ch. c. inf. and alk. vap.	187	V. sl.	30	Nil	Nil	Nil	Nil
19	Acid Malic	M. and sub.	Abt. 180	1	1½	Nil	Nil	Nil	Nil
20	Acid Meconic	Ch. c. wh. sub. and vap.	—	Sl.	48	Nil	Nil	Nil	Nil
21	Acid Nucleinic	Ch. c. od. of burnt feathers.	—	Al- most insol.	Insol.	Nil	Nil	Nil	Nil
22	Acid Oleic	Distils c. sl. residue, ch.	—	Insol.	55	Nil	Nil	Nil	Nil

No.	BROM. AQ.	SPECIAL TESTS.
12	Nil	0.0025 g. oxidised c. KMnO_4 gives benzaldehyde od. Can be reduced by sodium amalgam to hydrocinnamic acid (β -phenylpropionic acid). Detected in presence of benzoic acid by suspending in 5% uranium acetate solution and exposing to sunlight—in a few minutes od. of benzaldehyde is evolved, and brown ppt. forms.—Allen.
13	Nil	Denigé's Test: Add mercuric sulphate solution to the citrate sol. On warming, this solution decolorises KMnO_4 , giving white ppt. Visible 0.001 g. in 5 ml. wtr. Tartaric acid gives none. A solution is boiled with a little $\text{K}_2\text{Cr}_2\text{O}_7$, and, after cooling, acetic acid and sodium nitroprusside added and then AmOH to form a layer. Acetone from the citric acid gives a violet-red col. at the surface of contact.— <i>J. chem. Soc. Abstr.</i> , ii/1925, 246.
14	Yell. ppt.	Melted with KOH gives salicylate and acetate. Aqueous solutions of alkaline coumarates are fluorescent.
15	Wh. ppt.	0.0001 g. in 5 ml. wtr. turns brownish with $\text{NaNO}_2 + \text{HCl}$, changing to reddish-brown on adding a few drops NaOH sol.
16	Nil	Aq. sol. gives white ppt. with potassium antimonyltartrate solution. 0.000125 g. in 5 ml. wtr. on adding lime water gives pink; 0.00025 g. gives purple; 0.0005 g. gives blue-grey ppt. 0.005 g. in 5 ml. wtr. turns brown with NaNO_2 alone.
17	Nil	0.001 g. in 5 ml. wtr. boiled 3 mins. c. HCl gives phosphoric acid and glycerin.
18	Nil	Boil 0.01 g. a few minutes with 1 ml. NaOH and neutralise c. HCl . Half this sol. gives buff ppt. c. FeCl_3 (benzoate). Acidify the other, evap. to dryness, extract the glycoll c. ethyl acetate. This dissolves freshly pptd. copper carbonate c. deep blue colour. Copper benzoate if present does not interfere and if nec. benzoic acid can be removed with ether in which glycoll is insol.
19	Nil	Treated with potash and bromine, bromoform is formed.
20	Decols. first few drops	An aqueous solution with ferric chloride gives a red colour not discharged by hydrochloric acid or mercuric chloride (distinction from thiocyanate).
21	Nil	Decomp. on boiling c. dil. H_2SO_4 ; product yields phosphoric acid, carbohydrates and xanthine bases (xanthine, guanine, etc.).
22	Nil	Characteristic odour. Solidifies at 4° melting again at about 14° . Pure oleic acid, as such, does not redden litmus, but does in alc. sol. Nitrous acid converts it into the stereoisomeric elaidic acid, in crystalline leaflets, m.p. 45° .

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in—)	SOL. ALC. (1 in—)	MAY- ER'S.	GOLD CHL.	ACID PIC- RIC.	DRA
23	Acid Oxalic	M. and sub.	98–100	9	8	Nil	Nil	Nil	Sl. ppt.
24	Acid Salicylic	Sub. vap. brns.	158 –159	500	3	Nil	Nil	Nil	Nil
25	Acid Sclerotic	Ch., alk. vap. brns.	—	Prac. all	Insol.	Nil	Sl. br. ppt.	Nil	Red. br. ppt.
26	Acid Stearic	Sub., vap. brns.	50–55	Insol.	18	Nil	Nil	Nil	Nil
27	Acid Succinic	M. and vol.	Not below 185	20	9	Nil	Nil	Nil	Br. ppt.
28	Acid Sulphanilic	Ch., wh. vap. c. aniline od.	De- comp. at 280– 300	About 160	Insol.	Nil	Grad. dar- kens and gives ppt.	Nil	Nil
29	Acid Tannic	Part m., ch. c. or. sub. and br. inf. vap.	—	1½ slowly	1	Nil	Gr.- bl. ppt.	Nil	Nil
30	Acid Tartaric	M., ch., vap. brns.	162 –169	0·8	2½	Cry- stals. on stand- ing	Nil	Nil	Nil
31	Acid Valerianic	Evap. c. str. od., vap. brns.	—	30	All props.	Nil	Nil	Nil	Nil
32	Aconitine	Ch. c. acid vap.	196 –200 de- comp.	V. sl.	40	Wh. ppt.	Yell. ppt.	Yell. ppt.	Br. ppt.
33	Acriflavine	Dark-red ac. vap.	—	5	40	Buff ppt.	Red sol. fluor.	Buff ppt.	Br. ppt.
	Adalin, see Carbromal.								

O.	BROM. AQ.	SPECIAL TESTS.
3	Nil	A neutral salt sol. gives ppt. with CaCl_2 insol. in acetic acid but sol. in HCl . Ppt. c. dil. H_2SO_4 decolorises KMnO_4 on warming.
4	Wh. ppt.	Violet produced by 0·0000025 g. in 1 ml. wtr. c. 1 drop Fe Cl_3 is just visible; 0·000005 g. is distinct. Use narrow tube on white ground. Green copper salicylate by adding CuSO_4 to sol., not distinct for small qties. 0·00005 g. c. 0·5 g. Ca(OH)_2 htd. to redness in sm. tube gives phenol od.
5	Br. ppt.	Precipitated by tannic acid and phosphomolybdic acid.—Schmidt.
6	Nil	Acid number 200–210.
7	Nil	Forms fluorescein dyes when heated with resorcin and H_2SO_4 .
8	Wh. ppt. with excess	Neutral sol. of salt gives br. ppt. c. FeCl_3 ; when ppt. is washed, diss. in NH_4OH and sol. filtered, sol. gives ppt. c. BaCl_2 and equal vol. of alcohol.
9	V. s'ly stringy ppt.	Gives ppt. c. gelatin, $\text{Pb(NO}_3)_2$ (c. 0·0001 g.), $\text{Bi(NO}_3)_3$ (ditto), and ammoniacal copper solution (distinctions from gallic acid). 0·0001 g. gives bl. c. FeCl_3 . Is hydrolysed into gallic acid and dextrose by boiling with dilute sulphuric acid. Gives brown with NaNO_2 .
0	Nil	To a neutral sol. add AgNO_3 ; white silver tartrate is pptd. On just dissolving in dilute NH_4OH and warming, a silver mirror is obtained if test-tube is clean. To aq. sol. add 1 drop FeSO_4 , 3 drops H_2O_2 and excess NaOH —deep vi. colour.
	Nil	Has a characteristic, unpleasant odour. Fused CaCl_2 separates the acid from its aqueous solution. Zn and Ag salts are insol.
	Yell. ppt.	0·001 g. warmed c. 4 drops H_2SO_4 (sp. gr. 1·75) and a crystal of resorcin added, the liquid becomes reddish-violet in about 20 mins. 0·000001 g. produces tingling and numbing on the tongue. 0·0001 g. c. dil. acetic acid gives red ppt. c. KMnO_4 not changed c. bromine water.
	Nil	Dilute solution is yellow, strong solutions red with deep green fluorescence; gives HCl on heating with H_2SO_4 , as distinct from proflavine. Bulky yell. ppt. c. 10% sol. sod. salicyl.

NO.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in—)	SOL. ALC. (1 in—)	MAY- ER'S	GOLD CHL.	ACID PIC- RIC.	DR
34	Adrenaline	Reddish ch. c. alk. vap.	205 –212, de- comp.	V. sl.	V. sl.	Nil	Vi.	Nil	N
35	Æsculin	M. c. sl. eff., ch. c. yell. dist., vap. brns.	—	Sl.	Sl.	Nil	Blue col.	Nil	N
36	Albumin Tannate	Ch. c. od. of burnt feathers. Br. alk. vap. brns.	—	Sl.	Sl.	Nil	Dark dirty br. ppt.	Nil	N
37	Alcohol Methylic	Evap.	—	Misc.	Misc.	Nil	Nil	Nil	N
38	Aldehyde Abs.	Evap.	—	Misc.	Misc.	Nil	Nil	Nil	N
39	Allantoin	M., ch., alk. vap.	de- comp.	260	5,000	Nil	Nil	Nil	N
40	Allo- barbitone	Ac. vap. c. garlic od.	171 –172	Sl. sol.	Sl. sol. cold, v. sol. hot	Wh. cryst. ppt.	Nil	Yell. cryst. ppt.	N
41	Alloxan	M. to dark br. liq. ch., and HCN od.	—	Sl. sol.	Sl.	Nil	Sl. blue col.	Nil	N
42	Aloes Curaçao	Part m., br.-yell. vap. brns. br. dist.	—	Part sol.	6, in- com- plete	Nil	Red col.	Nil	Br pp
43	Aloes, Cape	Part m., br. vap. brns.	—	Part. sol.	2	Nil	Br. ppt.	Nil	Br pp
44	Aloes, Soc.	Part m., br.-yell. vap. brns., br. dist.	—	Part sol.	8, in- com- plete	Nil	Nil	Nil	Br pp

No.	BROM. AQ.	SPECIAL TESTS.
34	Nil	NaNO ₂ alone gives red colour. Reduces AgNO ₃ solution. Faintly acid sol. c. 0.25% FeCl ₃ sol. gives emerald-green colour; on gradual addition of NaHCO ₃ sol. colour changes through blue to red.
35	Dp. rd. col. to prplsh. opalescence	Yields dextrose and æsculetin on hydrolysis and then reduces Fehling's. Gives blood-red col. when treated with HNO ₃ and then excess of NH ₄ OH. Gives blue fluorescence in alk. sol. Treated with H ₂ SO ₄ and then sol. of NaOCl gives violet col.—Allen.
36	Nil	Nitrogen content 8%.
37	Nil	Oxid. c. chromic acid yields formic acid. Method of detection in ethyl alcohol, see ethyl alcohol, this vol.
38	Nil	Shaken c. conc. sodium bisulphite sol. gives cryst. addition-product, CH ₃ CH·OH·SO ₃ Na, decomposed by acid or alkali. Combines c. phenylhydrazine forming ethyldenenphenylhydrazone. Combines c. NH ₃ forming additive compound.
39	Nil	Conc. furfural sol. to which a little HCl added gives violet c. allantoin aq. sol. Mercuric nitrate (not chloride) gives a ppt. as c. urea.
40	Nil	0.1 g. in 1 ml. H ₂ SO ₄ gives yell. sol. changing slowly to dark red. 0.001 g. heated c. aq. sol. NaOH and acidified c. H ₂ SO ₄ gives CO ₂ c. acetic od. Satd. aq. sol. gives wh. ppt. c. Millon's reagent, sol. in excess.
41	Nil	Aqueous sol. slowly turns red when applied to the skin. Solid NaOH turns alc. sol. blue, which is decolorised by wtr.
42	Yell. ppt.	Curaçao aloes may be distinguished by the cupraloin reaction, not given by other varieties. To 10 ml. of 1 in 1000 aq. sol. add 1 ml. 5% CuSO ₄ and 1 ml. sat. NaCl sol. and a few drops of hydrocyanic acid—a deep claret col. is produced. Ammonia changes an alc. sol. of barbaloin and socaloin br.-red and nataloin carmine red. Filter through diatomite a 1% aq. sol. of aloes, and to 5 ml. of filtrate add 2 ml. HNO ₃ . Cape aloes gives yell.-br. changing rapidly to green; Curaçao aloes gives a deep brownish-red; Socotrine aloes gives a pale br.-yell.; and Zanzibar aloes gives a yell.-br.
43	Yell. ppt.	<i>Reactions given by all aloes:</i> Treat 0.5 g. with 100 ml. hot water, cool and filter. Heat 20 ml. of filtrate on w.b.c. small pieces of sod. peroxide. Brown coloration turning cherry-red produced which may be shaken out c. ether.
44	Yell. ppt.	Aloes distinguished from rhubarb, cascara, etc., by not being pptd. with basic lead acetate. Aq. sols. of aloes give a green fluorescence c. borax.

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in—)	SOL. ALC. (1 in—)	MAY- ER'S.	GOLD CHL.	ACID PIC- RIC.	DRAC
45	Aloin	M. and ch. vap. brns.	145	140	20	Nil	Red col.	Nil	Br. ppt.
46	Amido- pyrine	Brns. c. isonitrile od.	107 -109	18	About 2	Wh. ppt.	Vi. col.	Yell. ppt. re- diss.	Br. ppt.
47	Amydri- caineHydro- chloride	M. c. eff. then ch. Alk. vap. brns.	Abt. 169	1	4	Wh. ppt.	Buff ppt.	Yell. ppt.	Red- br. ppt.
48	Amyl Nitrite	Evaps., sl. res. ch.	—	Sl. sol.	Misc.	Br. col.	Nil	Nil	Blk. ppt.
49	Amyl Valerianate	Evaps., vap. brns.	—	V. sl.	Misc.	Nil	Nil	Nil	Nil
50	Amylene Chloral Sol. 1 : 1	Evaps., vap. brns.	—	Misc. c. 1. thrown out again c. 2, r'dis. in 3.	Misc.	Nil	Nil	Nil	Nil
51	Amylene Hydrate	Evaps.	—	8	Misc.	Nil	Nil	Nil	Nil
52	Amylocaine Hydrochlor.	M., vola- tilises c. od. of varnish	177 -179	2	3	Wh. ppt.	Yell. ppt.	Yell. ppt.	Buff ppt.
53	Aniline	Evaps.	—	30	Misc.	Nil	Dark br. ppt.	Nil	Br. ppt. to dirt yell.
54	Anthra- robin Antipyrin, see PHENA- ZONE	Br. sub., wh. res.	—	V. sl.	80	Nil	P'rple col.	Nil	Nil
55	Apiol (Green Liquid)	Becomes br., br. dist.	—	Prac. insol.	Part	Nil	Nil	Nil	Br. ppt.

No.	BROM. AQ.	SPECIAL TESTS.
45	Yell. ppt.	Dissolves in AmOH and caustic alks., the yellow sol. rapidly turning red c, green fluorescence. Ferric chloride to alc. sol. gives brown-green colour. One drop of CuSO_4 sol. added to 0.00005 g. in 5 ml. aq. gives yell. col. changed to red by 0.5 ml. satd. NaCl and to violet by 1 ml. 90% alc.
46	Vi. col.	AgNO_3 gives vi. col. followed by ppt. of metallic Ag. FeCl_3 gives bl.-vi. NaNO_2 and HCl give vi. col.
47	Yell. ppt.	Behaves similarly to cocaine, <i>q.v.</i> Can be distinguished by fact that 4% solution does not precipitate with platinic chloride in presence of HCl.
48	Nil	Characteristic odour—produces flushing of face on inhalation. For further information, <i>v.</i> Vol. I., p. 148 <i>et seq.</i>
49	Nil	Yields amyl alcohol and valeric acid on hydrolysis.
50	Nil	This is an oily liquid formed by adding chloral to amylene hydrate.
51	Nil	Has a pungent taste, and an odour resembling camphor and peppermint. B.p. 97° – 103° . It solidifies to crystals on cooling to a low temperature. Oxidation c. chromic acid gives acetone and acetic acid.
52	Yell. ppt.	Distinguished from cocaine by giving no ppt. c. KMnO_4 but decolorising it slowly. Aq. sol. gives ppt. on addition of I sol. (distinction from orthocaine) and c. Mayer's Reagent (distinction from orthocaine and benzocaine).
53	Wh. ppt.	To neut. or sl. alk. sol. add sodium hypochlorite or chlorinated lime sol.—purple violet, even in 1 in 26,000—changing to dirty red. Avoid excess of reagent. When this change has occurred, add ammoniacal phenol sol., return of blue col. even in 1 in 66,000. Aq. chromic acid sol. according to concentration gives green, blue or almost black.
54	Dirty br. ppt.	Easily soluble in caustic alkalis and ammonia, giving yellowish solution gradually changing to green or blue owing to formation of alizarin.
55	Nil	Occurs as a green liquid with peculiar odour and taste, and also as white crystals, m.p. 30° , with parsley-like odour. Sol. in H_2SO_4 c. blood-red col.

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in-)	SOL. ALC. (1 in-)	MAY- ER'S.	GOLD CHL.	ACID PIC- RIC.	DRAG.
56	Apocodeine Hydrochlor.	Smell of burnt feathers	Part at 90. De- comp. over 200	1	1	Dirty buff ppt.	Dirty br. ppt.	Yell. ppt.	Br. ppt.
57	Apomor- phine Hydrochlor.	Ch. c. wh. vap.	—	60	51	Wh. ppt.	Br. red ppt.	Yell. ppt.	Br. ppt.
58	Arbutin	M. c. sl. eff. then ch., br. dist. and vap. brns.	About 168	10	13	Nil	Gr. col. c'm'g slow- ly to br. ppt.	Nil	Nil
59	Arecoline Hydrobrom.	M. ch. alk. vap. brns.	About 167 -170	Sol.	Sol.	Pale yell. ppt.	Br.- red ppt.	Nil	Red- br. ppt.
60	Arsphena- mine	Ch., ac. vap. and od.	—	Read- ily	Sl.	Yell. ppt.	Or.	Yell. ppt.	Nil
61	Asparagin	Red-br. alk. vap.	—	50	Insol.	Nil	Nil	Nil	Nil
62	Aspriodine	M., ch. c. od. iodo- phenol	154	V. slight	16½	Nil	Nil	Nil	Nil
63	Atropine Methyl- bromide	M. c. sl. eff., ch., br. dist., irrit. vap.	About 222	1	8	Wh. ppt.	Red- yell. ppt.	Red- yell. ppt.	Red- br. ppt.
64	Atropine Methyl- nitrate	M., eff., ch., br. dist. and alk. vap. brns.	149 -150	1	4	Wh. ppt.	Crm. ppt.	Nil	Dull red ppt.
65	Atropine	M., sub., ch.	114 -116	300	3	Wh. ppt.	Buff ppt.	Yell. ppt.	Red- br. ppt.
66	Atropine Sulphate	M. and ch.	195 -196 when dry	0·5	3	Wh. ppt.	Buff ppt.	Yell. ppt.	Red. br. ppt.

BROM. AQ.	SPECIAL TESTS.
6 Dirty br. ppt.	Occurs usually as a yellowish or greenish-grey hygroscopic powder. Gives a characteristic blood-red colour with nitric acid.
7 Red ppt.	On adding ammon. persulph. and sod. bicarb. to aq. sol. and shaking c. CHCl_3 , the latter becomes a red or violet. Detects 1 in 100,000.— <i>J. chem. Soc. Abstr.</i> , ii/1924, 798. Acquires a gr. tint when exposed to light and air, and dissolves in nitric acid c. purple colour. Dil. aq. sol. c. NaHCO_3 gives ppt. which is wh. at first, becoming gr. Ppt. dissolves in alcohol (green), chloroform (blue) and ether (purple).
8 Yell. ppt. c. excess Br.	Hydrolysed by dilute sulphuric acid into dextrose and hydroquinone. Diazo Test—yellow with HCl and NaNO_2 turning red with sodium hydroxide.
9 Or.-yell. ppt. if not too dil.	Aq. sol. gives c. mercuric chloride sol. a white ppt. sol. in excess, the solution depositing colourless crystals on standing a few hours. Sulphuric and selenious acids give a bright yell. col. (distinction from pelletierine).
0 Nil	1 ml. of 1% sol. c. 1 drop 5% NaNO_2 gives or. colour. 0.5 ml. of resulting sol. c. 1 ml. 2% β -naphthol in 2N NaOH gives a clear wine-red sol.
1 Nil	In alk. sol. is lævorotatory; in acid, dextro. Copper hydroxide is dissolved on boiling, forming blue sol., depositing on cooling asparagin-copper, $(\text{C}_4\text{H}_7\text{N}_2\text{O}_2)_2\text{Cu}$. Insoluble in ether.
2 Nil	Heat c. H_2SO_4 gives off iodine. Heat c. NaOH , acidify and add FeCl_3 —violet colour.
3 Yell. ppt.	Gives Vitali's Reaction, <i>vide</i> atropine, and bromide reaction with silver nitrate.
4 Wh. ppt.	Gives reactions of atropine and a nitrate.
5 Orange ppt.	0.001 g. warmed with 2 ml. HgCl_2 in 50% alc. causes deposition of HgO (c. some Hg_2O)—Gerrard. Dilates the pupil even 1 in 130,000. 0.01 mg. responds to Vitali's Reaction.—Evap. a trace of atropine (or a salt) in a porcelain dish with a few drops of fuming HNO_3 ; a yell. residue is produced which on moistening with alc. KOH (1 in 10) produces a violet col. Strychnine does the same on applying 4% potash, but the col. is evanescent. Veratrine gives red-vi. or or.-red.
6 Orange ppt.	Gives aurichloride, m.p. 137° – 139° .

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in—)	SOL. ALC. (1 in—)	MAY- ER'S.	GOLD CHL.	ACID PIC- RIC.	DRAG.
67	Barbitone	M. and sub. entirely. Vap. brns.	189 –192	170	8.5	Nil	Nil	Nil	Nil
68	Barbitone, Soluble	Alk. vap. c. od. of alc. and NH ₃	—	5	Almost insol.	Nil	Nil	Nil	Buff ppt.
69	Beberine Sulphate	M., ch., vap. brns. c. phenol od.	—	About 1 in 1	Sl.	Buff ppt.	Br'n- ish ppt.	Yell. ppt.	Rec. ppt.
70	Benzamine Lactate	M. and evaps., vap. brns.	152 –156	5	8	Wh. ppt.	Crm. ppt.	Yell. ppt.	Rec. br. ppt.
71	Benzene	Evap., vap. brns.	About 0 re- melts at 4	Insol.	0.33	Nil	Nil	Nil	Nil
72	Benzocaine	M., evap., vap. brns.	90 –91	Sl.	8	Nil.	Br. ppt.	Nil	Nil
73	Benzyl Benzoate	Distils unchanged	20	Insol.	Misc.	Nil	Nil	Nil	Nil
74	Berberine Sulphate	M., ch., evolves nauseous wh. vap.	—	150	Sol.	Lem.- yell. ppt.	Br. ppt.	Lem.- yell. ppt.	Rec. br. pp.
75	Betaine HCl	Part m., ch. c. eff. and alk. vap. brns.	—	2	About 20	Nil	Nil	Cryst. ppt. conc. Nil in dil- ute.	Br. pp.
76	Beta- naphthol	M., ch., vap. brns. c. phenol od.	120 –122	1000	2	Nil	Nil	Nil	Nil
77	Beta- naphthyl Salicylate	M., turns yell., pt. evap., ch., vap. brns.	93– 95	Al- most insol.	Sl.	Nil	Nil	Nil	Nil

No.	BROM. AQ.	SPECIAL TESTS.
67	Nil	A satd. sol. acidified c. HNO_3 gives ppt. c. Millon's Reagent soluble in excess. When heated c. NaOH (solid or conc. sol.) NH_3 is evolved.
68	Decol.	Aq. sol. gives ppt. of barbitone on acidifying.
69	Red-br. ppt.	Contains 30% beberine, with other alkaloids.
70	Wh. ppt.	<i>Benzamine Lactate</i> and <i>Benzamine Hydrochloride</i> —0.1 g. in 1 ml. H_2SO_4 maintained at 100° for 5 minutes and cautiously diluted with 2 ml. wtr. gives aromatic od. and on cooling deposits crystals of benzoic acid. 0.05 g. c. 0.25 g. calomel does not blacken when moistened c. wtr. (distinction from cocaine HCl). 5 ml. of 1% sol. gives no permanent ppt. c. 5 ml. HgCl_2 sol. or c. 5 ml. KI sol. (distinction from cocaine and alphacaine respectively). 4% sol. hydrochloride gives sl. golden-br. ppt. c. plat. chlor., dissolving in HCl and separating again in crystals on standing.
71	Nil	To distinguish from petroleum benzine note solubility in alc.; benzene is sol. c. half vol. of alc. 90%, but petrol. benzine requires 5 to 6 vols. (using "Petrol," more). Warm 1 ml. c. 5–10 ml. of a mixture of 2 parts HNO_3 and 1 part H_2SO_4 ; benzene gives red vap., and yell. nitro-compds.; dilute c. 10–15 vols. wtr.—od. of bitter almonds. Petrol. benzine is scarcely affected. For Dragon's Blood Test, <i>vide</i> Vol. I, p. 309.
72	Yell. ppt.	1 ml. 1% aq. sol. c. trace HCl and 1 to 2 drops NaNO_2 sol. followed by 1 to 2 drops β -naphthol in NaOH —deep red colour and on standing, scarlet ppt.
73	Nil	Decomposes into benzyl alcohol and sodium benzoate on boiling with NaOH . Benzyl succinate melts at 45° .
74	Yell.-br. ppt.	To 5 ml. of 1% aq. sol. add 2 drops NaOH sol.; the liquid acquires an orange red colour but gives no ppt. On adding 4 drops acetone, it becomes turbid and gives yell. ppt. on standing.
75	Ppt. rediss. at first	Gold salt melts at 224° . Has a strongly acid reaction and taste. Fusion with KOH gives trimethylamine.
76	Wh. ppt.	Gives bluish fluorescence on adding 1 ml. solution of ammonia to 10 ml. sat. aq. sol.
77	Nil	Alcoholic sol. gives vi. colour c. FeCl_3 . Hydrolysis gives β -naphthol and salicylic acid. 0.1 g. added to 2 ml. H_2SO_4 gives lemon-yell. sol.; on addition of trace HNO_3 , colour changes to olive-green.

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in—)	SOL. ALC. (1 in—)	MAY- ER'S	GOLD CHL.	ACID PIC- RIC.	DRAG.
78	Bismuth Benzoate	Blk. c. yell. sub. and wh. vap. c. benzoic od.	—	Al- most insol.	Al- most insol.	Nil	Nil	Nil	Nil
79	Bismuth Citrate	Becomes blk. c. blk. sub.	—	Al- most insol.	Insol.	Nil	Nil	Nil	Nil
80	Bismuth Naphtho- late	Becomes blk. c. red-br. sub.	—	Insol.	Sl.	Nil	Nil	Nil	Nil
81	Bismuth Oxyiodo- gallate	Bec. blk. c. vap. of I	—	V. sl. Iodide and gallic acid go into sol.	In- com- pletely sol.	Nil	Yell. ppt.	Nil	Nil
82	Bismuth Salicyl- ate	Bec. blk., vap. c. od. of phenol, brns.	—	Al- most insol.	Al- most insol.	Nil	Nil	Nil	Nil
83	Bismuth Subgallate	Bec. blk. vap. brns.	—	Insol.	Insol.	Nil	Nil	Nil	Nil
84	Bismuth Tribromo- phenate	Yell. sub. at first, br. after	—	Insol.	Insol.	Nil	Nil	Nil	Nil
85	Bromal Hydrate	M., wh. vap., cols. flame green	54	2½	½	Nil	Nil	Nil	Nil
86	Brometone	M., sub. and ch. c. v. irrita- ting vap.	167	200	1	Nil	Nil	Nil	Nil
87	Bromo- form	Dist. then ch. c. br. vap. Bromine od.	—	Sl.	Misc.	Nil	Nil	Nil	Nil
88	Bromo- valerianyl- urea	M., ch., or. sub. and vap. brns.	145	Sl.	10	Nil	Nil	Nil	Nil

No.	BROM. AQ.	SPECIAL TESTS.
78	Nil	Identify bismuth in the residue and separate benzoic acid by heating salt with alkali, filtering and acidifying.
79	Nil	Sol. in AmOH and alkali citrates. Gives bismuth and citrate reactions.
80	Nil	Hydrolysis gives bismuth salt and β -naphthol.
81	Nil	Easily soluble in mineral acids and caustic alkalis. Gradually turns red in moist atmosphere. Concentrated H_2SO_4 liberates iodine vapour.
82	Yell. ppt.	Identify bismuth and salicylic acid—the latter by shaking powder with ether and dil. H_2SO_4 ; on shaking ethereal layer with wtr. containing trace of $FeCl_3$, a vi. colour is produced.
83	Nil	NaOH dissolves with yellow colour—turning red. Identify gallic acid by means of ferric chloride after removal of bismuth by suspending in water and passing H_2S .
84	Nil	Decomposed by acids giving bismuth salt and tribromophenol.
85	Nil	Decomposes at 100° to 110° into bromal and water.
86	Nil	Reacts like chlorbutol, <i>q.v.</i>
87	Nil	Has odour resembling chloroform, from which it is easily distinguished by sp. gr. and b.p.
88	Nil	Odour like bromal on heating. Dissolves in caustic alkali sol. and is pptd. by acids. After heating c. NaOH and acidifying residue c. H_2SO_4 , CO_2 liberated c. valerianic odour. Millon's gives ppt. (<i>cf.</i> Malourea). Nessler's Reagent c. satd. solution gives only slight colour and ppt. (<i>cf.</i> Adalin), but after fusing c. KOH and dissolving in water there is the usual effect.

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in-)	SOL. ALC. (1 in-)	MAY- ER'S.	GOLD CHL.	ACID PIC- RIC.	DR.
89	Butyl- chloral Hydrate	Sub. totally	Abt. 78	43	0·6 c. com- bina- tion.	Nil	Nil	Nil	Nil
90	Caffeine	Sub. and m.	235 -237 (dried at 100)	80	40	Nil	Sl. ppt.	Nil	Br. ppt
91	Caffeine Citrate	M., ch., br. dist. and sl. vap. brns. c. phenol od.	Abt. 160	32	25	Nil	Sl. ppt.	Nil	Br. ppt.
92	Caffeine and Sodium Benzoate	M., ch. Wh. sub., vap. brns. c. od. of phenol and benzene	—	About 1	40	Nil	V. sl. ppt. on stand- ing	Nil	Yell. br. ppt.
93	Caffeine and Sodium Salicylate	Part m., sub. c. alk. vap. and phenol od.	—	1	28	Nil	Nil	Nil	Br. ppt.
94	Calcium Acetyl- salicylate	M., ch., od. of phenol and salicylic esters	—	6	800	Nil	Nil	Nil	Yel ppt.
95	Calcium Glycero- phosphate	Ch., acrid vap., brns.	—	About 50	Al- most insol.	Nil	Nil	Nil	Nil
96	Calcium Lactate	M., swells and ch.	—	About 20	Insol.	Nil	Nil	Nil	Nil
97	Calcium Sacchar- ate	Ch. c. caramel od.	—	10	Insol.	Nil	Sl. yell. ppt.	Nil	Sl. br. ppt
98	Calcium Sodium Lactate	Liquefies, boils, ch., wh. vap. brns.	—	About 15	About 10	Nil	Nil	Nil	Nil
99	Camphor Mono- brom.	M. c. camph. od. and sub.	74 -76	Insol.	12	Nil	Nil	Nil	Nil
100	Canthari- din	M., sub., vap. brns.	216 -218	1100	Sl.	Nil	Nil	Nil	Nil

BROM. AQ.	SPECIAL TESTS.
Nil	Nitric acid converts it into trichlorbutyric acid, m.p. 44°
Nil	On evaporating 0.0001 g. to dryness with bromine water a reddish-brown spot is obtained, which turns violet-red with NH_3 vapour (Murexide Reaction). Aq. sol. c. N/10 iodine gives no ppt. unless acidified c. HCl.
Nil	The aqueous solution is acid owing to hydrolysis. All the citric acid present can be titrated with caustic soda, using phenolphthalein as indicator. Murexide test as above.
Nil	Gives reactions of caffeine and sodium benzoate. Caffeine can be extracted with chloroform from alk. sol.
Wh. ppt.	Gives reactions of caffeine and sodium salicylate. Caffeine can be estimated by extraction with chloroform from alk. sol.
Wh. ppt.	HCl ppts. aspirin; filtrate gives reactions for Ca. After hydrolysis, gives reactions for salicylic acid.
Nil	Identify calcium and phosphate after hydrolysis with acid.
Nil	Acidify a 1 in 20 solution with sulphuric acid, add potassium permanganate and heat—the odour of acetaldehyde is developed.
Nil	To a suspension of a small quantity in 10 ml. of water add 5 ml. HCl and 0.1 g. resorcin in 5 ml. After shaking, place in boiling water 5 minutes—pink to deep red colour. When used in cream it can be detected thus, using 10 ml.
Nil	Gives reactions of calcium and sodium. On warming with potassium permanganate gives acetaldehyde.
Nil	Alc. KOH has no action, but silver oxide in presence of CHCl_3 decomposes it. Heated with 4 times its quantity of HNO_3 on sand-bath forms camphoric acid and bromonitrocamphor—rhombic prisms almost insol. in alcohol, m.p. 105°.
Nil	Boiled with soda and potash forms cantharidates. An exceedingly minute quantity of cantharidin will produce a blister.

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in -)	SOL. ALC. (1 in -)	MAY- ER'S.	GOLD CHL.	ACID PIC- RIC.	DE
	Carbamide (see Urea)								
101	Carbromal	Part sub., ac. vap.	116 -118	3000 (more sol. in hot)	About 18	Nil	Crys. ppt. (No ppt. c. 1 in 1000)	Crys. ppt. (No ppt. c. 1 in 1000)	Pp (N pp c. in 100
102	Chloral Forma- mide	M., sub. c. chloral od.	122 -126	21	2	Nil	Nil	Nil	N
103	Chloral Hydrate	M., sub. c. distinc- tive od.	50 -58	0·25	0·2	Nil	Nil	Nil	N
104	Chloramine	Ac. vap. od. of <i>p</i> -toluene- sulph.- chlor.	De- comp.	7	12 c. de- comp.	Yell. col. folld. by ppt.	Nil	Yell. sol., gr. fluor.	B tar pp
105	Chlorbutol	Wh. sub. and irrit. vap.	80	125	1	Nil	Nil	Nil	N
106	Chrysa- robin (Chrysopha- nic Acid)	M., ch., yell. vap. brns.	About 155 -165	V. sl.	Sl.	Nil	Nil	Nil	N
107	Cimici- fugin	Br. dist., vap. brns.	—	Sl.	1	Nil	Nil	Nil	S b pp
108	Cinchoni- dine	M., ch., and alk. vap. brns.	202	V. sl.	16	Wh. ppt.	Buff ppt.	Yell. ppt.	Re b pp
109	Cinchoni- dine Sulphate	Ch. c. vi. distillate then yell. c. od. of H ₂ S	About 207 when an- hyd.	100	60	Wh. ppt.	Buff ppt.	Yell. ppt.	Re b pp
110	Cinchonine	M., ch. c. burnt feather od. Vap. brns.	255	V. sl.	175	Wh. ppt.	Buff ppt.	Yell. ppt.	R b pp

BROM. AQ.	SPECIAL TESTS.
Nil	H_2SO_4 gives HBr on warming. H_2SO_4 c. MnO_2 gives Br. Heated c. dil. NaOH, NH_3 is evolved and NaBr formed. Does not give ppt. c. Millon's reagent after acidifying (<i>cf.</i> barbitone). Sat. aq. sol. gives yell. c. Nessler's reagent and then orange ppt. (Allobarbitone, barbitone and propional do not react unless fused c. KOH previously; bromoisovaleryl carbamide and phenobarbitone give only a faint colour.)
Nil	Water slightly warm decomposes it. Caustic alkalis decompose it into chloroform, ammonia and alkali formate. Dilute acids have no action on it.
Nil	Compounds containing the group CX_3 ($\text{X}=\text{Cl}$, Br, or I) on heating with 20% NaOH and pyridine give a red col. which passes into pyridine layer. Reaction detects less than 0.005 mg. of chloral hydrate or chloroform.— <i>J. chem. Soc. Abstr.</i> , ii/1924, 352.
Wh. ppt.	Warmed with NaOH and aniline gives phenyl isocyanide od. Liberates iodine from aq. sol. KI. Does not liberate Br from neutral sol. NaBr and gives wh. ppt. c. HgCl_2 sol. (distinction from dichloramine).
Nil	Gives phenyl isocyanide od. on warming c. aniline and sodium hydroxide solution. Iodoform is produced on shaking with iodine and dilute sodium hydroxide solution.
Nil	Partially soluble in KOH sol. c. red colour, the solution showing gr. fluorescence when greatly diluted. Allen gives tests to distinguish chrysophanic acid from chrysarobin. (m.p. of commercial samples varies.)
V. sl.	General characters. No chemical test.
Ye.l. ppt.	Gives neither thalleioquin test nor the $\text{K}_3\text{FeC}_6\text{N}_6$ modification (<i>cf.</i> Cinchonine). Soluble in large amounts of ether. Sodium potassium tartrate in neutral solution of a salt gives white precipitate.
Yell. ppt.	Gives reactions of cinchonidine and sulphate. 0.0001 g. gives ppt. c. Drag., Mayer's, etc.
Yell. ppt.	Only slightly sol. in ether (1 in 370). Few characteristic reactions. Not pptd. by NaHCO_3 in presence of tartaric acid (quinine and cinchonidine are). Does not give thalleioquin test nor red col. with $\text{K}_3\text{FeC}_6\text{N}_6$ and ammonia on addition of these to acetic acid sol. after treating with Br (distinction from quinine and quinidine). Not rendered fluorescent by very dilute H_2SO_4 .

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in-)	SOL. ALC. (1 in-)	MAY- ER'S	GOLD CHL.	ACID PIC- RIC.	DRA
111	Cinchonine Hydro- chlor.	Ch. c. vi. distillate vap. brns.	217- 218 when an- hyd.	22	1	Wh. ppt.	Buff ppt.	Yell. ppt.	Re br ppt
112	Cincho- phen	Ch. c. choking vap.	214- 217	Insol.	Sl.	Nil	Nil	Nil	Br ppt
113	Cinnamic Aldehyde	Evap. Res. ch. Vap. brns.	—	Sl.	Misc.	V. sl. ppt.	Nil	Nil	Re br ppt
114	Cocaine	M. c. yell. dist., ch., vap. brns.	97 -98	V. sl.	10	Wh. ppt.	Buff ppt.	Yell. ppt.	Re br ppt
115	Cocaine Hydro- chlor.	M. c. eff. to yell. liq., ch. and alk. vap. brns.	182 de- comp.	0.5	2½	Wh. ppt.	Yell. ppt.	Yell. ppt.	Re br ppt
116	Codeine	M., ch. c. od. of NH ₃ ; vap. brns.	155- 156 when an- hyd.	120	2	Wh. ppt.	Lt. br. ppt.	Yell. ppt. bec. bl.- blk.	Re br ppt
117	Codeine Phos- phate	M., ch., od. of NH ₃ , vap. brns.	—	30	26	Wh. ppt.	Lt. br. ppt.	Yell. ppt.	Re br ppt
118	Colchicine	M. c. decomp., ch., alk. vap. brns.	About 145 when dry	1	1	Sl. ppt.	Buff ppt.	V. sl. yell. ppt.	Br pp
119	Colchicine Salicy- late	M. c. de- comp., ch., alk. vap. brns.	55- 60	Sl.	1	Sl. ppt.	Buff ppt.	V. sl. yell. ppt.	Br pp
120	Collargol	Br. sub. and alk. vap. brns.	—	25	Insol.	Blk. ppt.	Blk. ppt.	Dk. br. ppt.	Or pp
121	Coniine Hydro- brom.	M. and evaps. c. br. dist.	About 212	2	3	Crm. ppt.	Or.- red ppt.	Nil	D dirt re pp
122	Cotarnine Chloride	M. to deep red liq., ch. and br. alk. vap. brns.	About 125	Less than 0.5	3	Yell. ppt.	Buff ppt.	Yell. ppt.	Re br pp

D.	BROM. AQ.	SPECIAL TESTS.
1	Pale yell. ppt.	Gives reactions of cinchonine and hydrochloride. Differs from cinchonidine in being dextrorotatory.
2	Nil	Sat. sol. in hot HCl gives br. cryst. ppt. c. plat. chlor. sol. Ammoniacal sol. evaporated to small bulk and diluted c. wtr. gives a wh. ppt. c. AgNO ₃ , a yell. ppt. c. Pb acetate and a gr. ppt. c. CuSO ₄ .
3	Flocc. ppt.	B.p. 253° to 254°. Oxidised by KMnO ₄ and acid into benzaldehyde and benzoic acid.
4	Yell. ppt.	<i>See Cocaine HCl.</i>
5	Yell. ppt.	Addition of 1 to 2 drops chromic acid sol. to 1% cocaine gives a yell. ppt. re-diss. on shaking; with more chromic acid ppt. is permanent. See also in Analytical Memoranda.
6	Yell. ppt.	Does not reduce iodic acid (distinction from morphine). No blue colour with ferricyanide and ferric chloride (distinction from morphine). 0.001 g. warmed with 1 ml. H ₂ SO ₄ and 2 drops FeCl ₃ sol. gives deep blue colour. Greenish-blue with Froehde's Reagent.
7	Yell. ppt., re-diss. at first	Gives reactions of codeine and phosphate.
8	Buff ppt.	Only slightly sol. in ether or benzene. Practically insol. in light petroleum. H ₂ SO ₄ with a trace of HNO ₃ added gives yell.-gr., changing through blue-vi. and wine-red to yell. Chlorine wtr. gives yell ppt. c. aq. sol. colchicine soluble in AmOH with or. colour. NaNO ₂ +HCl give dirty br.
	Buff ppt.	Gives reactions of colchicine and salicylic acid.
	Yell. ppt.	A substance having a black or metallic appearance and containing about 90% silver.
	Yell. ppt.	With conc. H ₂ SO ₄ gives a blood red colour turning green. This liquid alkaloid is distinguished from nicotine by giving no ppt. with platinic chloride, and a deep red col. with alk. sol. of phenolphthalein.
	Yell. ppt.	0.3 g. dissolved in 5 to 15 ml. water and N/10 iodine sol. added, gives brown ppt., which dried over H ₂ SO ₄ melts at 142° to 144°. Cotarnine dissolves in conc. HNO ₃ with formation of a red sol. and oxalic acid.

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in-)	SOL. ALC. (1 in-)	MAY- ER'S.	GOLD CHL.	ACID PIC- RIC.	DRA
123	Cotarnine Phtha- late	M. to deep red liq. Ch. br. dist. and alk. vap. brns.	About 113	0·5	5	Crm. ppt.	Buff ppt.	Yell. ppt.	Rec br. ppt.
124	Coumarin	M. and evap., vap. brns.	68 -70	Sl.	7	Nil	Nil	Nil	Blk resi- nous ppt
125	Cryogenine	M., ch., str. alk. vap. brns.	170	100	25	Nil	Blk.- br. ppt.	Nil	Br.- yell. cryst als form slow ly
126	Cubebin	M., ch. c. br. dist. and vap. brns.	128	V. sl.	Sl.	Nil	Nil	Nil	Nil
127	Dextrose	Ch., burnt sugar od., br. sub.	—	Misc.	Sl.	Nil	Nil	Nil	Nil
128	Diamor- phine	M. then ch., alk. vap. brns.	169	800	44	Sl. wh. ppt.	Sl. buff ppt.	Sl. yell. ppt.	Rec br. ppt
129	Diamor- phine Hydrochlor.	M. to br. liq. c. sl. eff., alk. vap. brns.	233	2½	13	Wh. ppt.	Dirty yell. ppt.	Yell. ppt.	Rec br
	Dial (<i>see</i> Allobarbi- tone)								
130	Dichloram- ine	M. then explodes; od. of <i>p</i> - toluene- sulph.- chlor.	About 78	Al- most insol.	Sol. c. de- comp.	Deep red	Nil	Yell. ppt. c. gr. fluor- esc.	Ni
131	Digitalin	Swells ch. c. caramel od.	—	Read- ily	Read- ily	Nil	Nil	Nil	N

O.	BROM. AQ.	SPECIAL TESTS.
3	Dark yell. ppt.	Decompose salt and identify the alkaloid and phthalic acid.
4	Deep yell. ppt.	Has a characteristic fragrant od. and sublimates at 100°. Dissolves slowly in hot NaOH sol. c. a slight gr. col., excess of acid reprecipitating coumarin. Satd. aq. sol. c. iodine sol. gives a br. flocculent ppt. which coagulates to a dark green mass on shaking.
5	Nil	The addition of 1 drop of ferric chloride to solution in conc. H ₂ SO ₄ gives deep red colour.
6	Nil	Oxidised by alk. KMnO ₄ to piperonylic acid and oxalic acid.—Schmidt.
7	Nil	Specific rotation of well-boiled 10% aq. sol. about +52°. Reduces aq. sol. AgNO ₃ on warming. In addition to Fehling's, Barfoed's Reagent (warm) is also reduced (distinction from dextrin and maltose). Na, Ca and Ba oxides form saccharates sol. in aq. Ferments c. yeast (useful confirmatory test).
8	Yell. ppt.	Gives yellowish red c. H ₂ SO ₄ and a little HNO ₃ , darkening on warming. From acid solns. is pptd. by caustic alkalis, ammonia and ammon. carb., redissolved by the first in excess. Does not reduce iodates (distinction from morphine). <i>See also</i> the hydrochloride.
9	Yell. ppt.	Dissolve 0.05 g. in 5 ml. water; add 3 drops FeCl ₃ (5 : 100); no blue col. (distinction from morphine). Nitric acid dissolves c. yell. colour changing to bl. on warming and becoming yell. again on cooling. Sol. in conc. H ₂ SO ₄ warmed, cooled, diluted c. wtr. and treated c. sol. K ₃ FeC ₆ N ₆ containing trace FeCl ₃ gives deep blue colour. Morphine, ethylmorphine and codeine do not yield this reaction.
	Wh. ppt.	Ppt. c. proteins. Sol. in alc., ether and cottonseed oil, but decomposes them. Readily sol. in chlorof. and eucalyptus oil without evident change. Dissolves in solutions of fixed alkalis forming the soluble monochloramine. Strong oxidising agent, liberating iodine from KI. Gives no ppt. c. HgCl ₂ (<i>cf.</i> chloramine).
	Nil	1 mg. in 1 ml. glacial acetic acid containing trace of ferric chloride layered on to sulphuric acid gives reddish band. Usually adjusted to standard strength by admixture with lactose.

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in—)	SOL. ALC. (1 in—)	MAY- ER'S.	OLD CHL.	ACID PIC- RIC.	DRA
132	Digitoxin	M., ch., yell. dist., vap. brns.	About 240	Insol.	140	Nil	Nil	Nil	Ni
133	Disodium Methyl- arsonate	Ch., blk. sub., garlic od.	—	1	350	Nil	Nil	Nil	Ni
134	Elaterin	M. to yell. liq.	209	Insol.	160	Nil	Nil	Nil	Ni
135	Emetine	Part m. and ch., alk. vap. burns	About 74	Sl.	3	V. sl. wh. ppt.	V. sl. dirty crm. ppt.	Sl. yell. ppt.	Dk red br pp
136	Emetine and Bismuth Iodide	Blackens	—	Insol.	Insol.	Yell. ppt.	Br. ppt.	Yell. ppt.	Br pp
137	Ephedrine	M., boils, vap. brns., od. of bitter almonds	About 40	Read- ily	Read- ily	Wh. ppt.	Yell. ppt.	Nil	Br pp be yell wh
138	Ephedrine Hydro- chlor.	M. and gives arom. od., ch.	215	5	About 5	Nil, wh. if conc.	Nil	Nil, yell. if conc.	Re br pp
139	Ergotinine	Ch. c. part fusion	Ch. at about 239	Insol.	Sl.	Nil	Nil	Nil	N
140	Ergotoxine	Ch., br. vap. brns., od. of burning meat	Ch. at 150 —160	V. sl.	Sol.	Sl. ppt.	Nil	Nil	N
141	Ergotoxine Ethane- sulph.	M. to br. liq., br. vap., od. of burning meat	Ch. at 170— 180	Sol.	Sol.	Wh. ppt.	Buff ppt.	Yell. ppt.	R b pp
142	Erythrityl Tetrani- trate	M. and then explodes	61	Insol.	About 90	Nil	Nil	Nil	N

	BROM. AQ.	SPECIAL TESTS.
2	Nil	(See Digitalis this vol.) HCl (sp. gr. 1.19) dissolves it in cold s. colour, but on warming it dissolves c. brown col. To 0.0001 g. in Petit's Liq. add 2 ml. acetic acid and 1 drop 5% FeCl ₃ and layer on conc. H ₂ SO ₄ —br. ring, blue-gr. above.
3	Nil	0.0005 g. in 5 ml. water gives wh. ppt. with silver nitrate, a vi. ppt. with cobalt nitrate and a wh. ppt. on warming with calcium chloride (distinction from sodium cacodylate).
4	Nil	With Froehde's Reagent, first green then brown col. Mandelin's Reagent gives bl. A sol. of about 0.01 g. in 5 ml. of melted phenol becomes crimson, changing to scarlet on adding a few drops of H ₂ SO ₄ .
5	Sl. dark yell. ppt.	Sulphomolybdic acid gives brown colour, changed to blue by HCl. 0.0002 g., e.g., in Tinct. Ipecac. gives yell. c. HCl and H ₂ O ₂ .— <i>Pharm. J.</i> , i/1928, 495.
6	Br. ppt. sol. in excess	Gives reactions for bismuth and iodine. Quickly loses its red colour on shaking with sodium bicarbonate and (more slowly) with 0.2% HCl.
7	Or.-yell. ppt.	0.01 g. in 1 ml. water with 0.1 ml. aq. sol. copper sulphate and 1 ml. sodium hydroxide gives violet colour; on shaking mixture c. ether, latter becomes purple and aq. sol. brown. Gives the hydrochloride on standing in contact c. chloroform and evaporating. 0.01 g. in 1 ml. water with 1 ml. K ₃ FeC ₆ N ₆ sol. and 1 ml. potassium hydroxide gives benzaldehyde od.
8	Yell. ppt. re-diss. and repptd. by excess	Gives reaction for hydrochloride, and with copper sulphate reacts as ephedrine.
9	Nil	Gives same colour reactions as ergotoxine.
0	Br. yell. ppt.	Dil. aq. sol. mixed c. 0.125% sol. <i>p</i> -dimethylaminobenzaldehyde in 65% <i>v/v</i> sulphuric acid containing a trace of ferric chloride gives a blue colour. Sol. in glacial acetic acid containing a trace of ferric chloride gives purple-blue on adding 1 to 2 drops sulphuric acid.
1	Br.-yell. ppt.	Gives reactions of ergotoxine. The acid radicle can be estimated by dissolving in methyl alcohol, diluting, and titrating with N/10 KOH, using phenolphthalein.
2	Nil	Usually occurs mixed with lactose, from which it can be separated by extraction c. alc. Residue obt. on evaporating alc. sol. explodes on percussion.

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in-)	SOL. ALC. (1 in-)	MAY- ER'S	GOLD CHL.	ACID PIC- RIC.	DRA
143	Ethylmor- phine Hydrochlor.	M. c. eff. and gives fishy od.; ch., vap. burns	About 123	10	25	Wh. ppt.	Br. yell. ppt.	Yell. ppt.	Br. ppt.
	Eucaïne Lactate (see Benza- mine Lactate)								
144	Eucalyptol	Evaps., vap. brns. and eu- calyptus od.	—	Sl.	Misc.	Nil	Nil	Nil	Br. ppt.
145	Euflavine	Br. dist.; red vap., c. od. of NH ₃	—	Sl.	Sl.	Or. ppt.	Br. col. or ppt.	Or. ppt.	Br. ppt.
146	Fluoresceïn (Soluble)	Part m., turns br.- gr., ch. and swells up	—	Less than 1	5	Blk. ppt.	Yell.- br. ppt.	Yell. ppt. re- dis.	Blk. ppt. bec. br.
147	Formalde- hyde Solution	Boils, gives gas, brns. blue, sl. res., ch.	—	Misc.	Misc.	Nil	Nil	Nil	Nil
148	Fuchsine	Part m. and br. vap. brns.	—	Sl. sol.	About 20	Dk. ppt. sol. turns vi. pink	Dk. ppt. sol. turns pur- ple	Br. ppt. sol. turns yell.	Dk. ppt. sol. turns gr.
149	Gelsemine	M., ch., br. dist., and alk. vap. brns.	About 178	Sl. Sol.	Sol.	Wh. ppt.	Lt. br. ppt.	Yell. ppt.	Br. ppt.
150	Glycogen	Ch., br.- yell. vap. brns.	—	About 2 in- com- plete	Al- most insol.	Nil	Nil	Yell. ppt.	Sl. red. br. ppt.
151	Guaiacol	Evap. c. charact. od., vap. brns.	Cryst. form 28	80	Misc.	Nil	Nil	Nil	Br. ppt.

D.	BROM. AQ.	SPECIAL TESTS.
3	Yell. ppt. rediss. at first	Does not give blue col. c. FeCl_3 or reduce iodates direct. 0.01 g. dissolved in 10 ml. H_2SO_4 after liberation of the HCl , gives a clear sol., which on adding a drop of FeCl_3 sol. and warming turns violet or blue, changing to red on adding 2 to 3 drops of HNO_3 . The free base is less soluble in AmOH than <i>Codeine</i> . Such sol. re-ppts. the base in crystals melting at 93° . It is distinguished from morphine in that on adding it to $\text{K}_3\text{FeC}_6\text{N}_6$ sol. c. FeCl_3 it does not give an immed. blue, but a bluish-green colour.
4	V. sl. ppt. re-diss. at first	1 ml. in a freezing mixture c. eq. vol. of phosphoric acid added gradually gives a white crystalline mass of eucalyptol phosphate. If warm water be then added eucalyptol will separate. Agitated c. strong sol. of iodine in potassium iodide a pasty mass is produced in which green lustrous crystals are formed.
5	Red ppt.	Bulky yell. ppt. on adding sodium salicylate to aq. sol. No effervescence with sodium bicarbonate (<i>cf.</i> acriflavine). No ppt. c. solution of formaldehyde (<i>cf.</i> proflavine).
6	Or. red ppt.	Unmistakable fluorescence in sol. Col. discharged by acid. Heated c. zinc dust and NaOH reduced to colourless fluorescin.
7	Nil	Adds AmOH . Reduces amm. silver nitrate sol. (mirror). Responds to Schiff's Reagent. <i>See also</i> Milk Tests, Urine Tests and Paraformaldehyde.
8	Almost bl. ppt. floats, liq. decol.	Is decolorised by zinc and HCl also by sulphurous acid. For detection of minute quantities as in urine, ext. with acetic ether or amyl alc. The colour in these disappears on adding AmOH or HCl if fuchsine present.
9	Yell. ppt.	0.001 g. gives green col. with conc. nitric acid. 0.001 g. c. sulphuric acid and $\text{K}_2\text{Cr}_2\text{O}_7$ gives reddish-violet turning green.
10	Sl. wh. ppt.	Iodine gives burgundy-red colour. Readily soluble in alkalis. Dilute acids convert it into dextrose, but prior to that treatment does not reduce Fehling.
11	Dark orange ppt.	Occurs in crystalline form, or as a liquid (sp. gr. about 1.12; b.p. 200° to 205°). Characteristic odour and taste. An alcoholic solution with ferric chloride gives emerald-green colour changing to blue and then brown. Gives yellow and not red.-br. on shaking c. 10 vols. of H_2SO_4 (distinction from creosote).

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in-)	SOL. ALC. (1 in-)	MAY- ER'S.	GOLD CHL.	ACID PIC- RIC.	DRA
152	Guaiacol Benzoate	M. and evap., vap. brns.	50-52	Almost insol.	50	Nil	Nil	Nil	Ni
153	Guaiacol Carbonate	M. and evaps. almost entirely, vap. brns.	86	Nil	About 200	Nil	Nil	Nil	Ni
154	Guaiacol Cinnamate	M. to clear liq., bec. br. c. yell. sub. and vap. brns.	130	Insol.	Sol.	Nil	Nil	Nil	Ni
155	Hexamine	Sub., m. or ch. brns. in air	—	1½	8	Nil	Dirty yell. ppt.	Cryst. ppt.	Br. blk. ppt.
156	Hexyl-resorcinol	M., boils	Abt. 66	2000	Read-ily	Nil	Blk. ppt.	Nil	Ni
157	Holocain Hydrochlor.	M., bec. yell., ch., yell. dist. vap. brns. c. gr. flame	186-189	55	8	Wh. ppt.	Buff ppt.	Yell. ppt.	Br. ppt.
158	Homatropine Hydrobrom.	M., colourless then ch., br. dist., alk. vap. burns	214	6	18	Wh. ppt.	Buff ppt.	Nil	Br. ppt.
159	Hydrastine Hydrochlor.	M., ch., alk. vap. brns.	168 if dry	—	120	Sl. cloud	Nil	Nil	Sl. br. ppt.
160	Hydrastinine Hydrochlor.	M. to yell. liq., ch. br. dist., vap. brns.	About 210	Less than 1	About 3	Crm.-wh. ppt.	Buff ppt.	Yell. ppt.	Re. br. ppt.
161	Hyoscine Hydrobrom.	M., ch., br. dist., and alk. vap. brns.	—	About 2	13	Wh. ppt.	Br.-yell. ppt.	Yell. ppt.	Re. br. ppt.
162	Hyoscyamine Sulphate	M., ch., and alk. vap. brns.	203-206	½	4½	Wh. ppt.	Yell. ppt.	Yell. ppt.	Re. br. ppt.

	BROM. AQ.	SPECIAL TESTS.
2	Nil	When hydrolysed gives reactions for guaiacol and benzoic acid.
3	Nil	0.01 g. gives guaiacol and potassium carbonate on hydrolysis with alcoholic potash.
4	Nil	When hydrolysed gives reactions for guaiacol and cinnamic acid.
5	Yell. ppt.	Boiled with dilute acids gives formaldehyde and ammon. salt. Gives ppt. c. HgCl_2 sol. becoming cryst. on standing.
6	Wh. ppt.	Paraffin odour on heating. H_2SO_4 cold dissolves, hot ch. and SO_2 evolved. HNO_3 gives violent reaction. Trace FeCl_3 added to alcoholic sol. gives gr. colour.
7	Yell. ppt.	Yellow waxy ppt. with NaNO_2 and HCl .
8	Yell. ppt.	Alkaloidal base, obt. by adding AmOH to aq. sol., shaking out c. CHCl_3 and evaporating solvent, melts at about 98° and when warmed c. 2% sol. HgCl_2 in alcohol (60%) gives yell. ppt. becoming brick-red. Does not react to Vitali's test—0.0001g. gives yell. instead of violet given by atropine, <i>vide</i> atropine. Does not ppt. c. tannic acid or platinic chlor. after adding HCl .
9	Sl. cloud	Froehde's Reagent gives gr. to br. colour. Sulphovanadic acid gives orange-red. H_2SO_4 c. trace of molybdic acid gives gr. colour changing to br. H_2SO_4 c. trace of $\text{K}_2\text{Cr}_2\text{O}_7$ gives light gr. colour changing to br. To distinguish from hydrastinine, <i>see</i> this Vol., p. 127.
0	Yell. ppt.	Aq. sol. acidified c. H_2SO_4 has blue fluorescence. With Nessler's Reagent gives black ppt. of mercury.
1	Yell. ppt.	Response to Vitali's Reaction very similar to that of atropine, <i>q.v.</i> Gold chloride compound obt. by dissolving separated base in HCl , adding sol. auric chloride and recryst. from water has m.p. of 198° to 200° .
2	Yell. ppt.	Response to Vitali's Reaction very similar to that of atropine, <i>q.v.</i> Gold salt (recrystallised from hot aq.) is in golden shining leaflets, m.p. 165° ; sols. reduce in the light. A 1 in 20 sol. does not ppt. c. platinic chlor. sol. (distinction from most alkaloids).— <i>U.S.P. X.</i>

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in-)	SOL. ALC. (1 in-)	MAY- ER'S.	GOLD CHL.	ACID PIC- RIC.	DR.
163	Hypnal	M. c. chloral od., ch., and gives alk. inflam. vap.	67 -68	10	About $\frac{1}{2}$	Sl. wh. cloud	Buff ppt.	Yell. ppt.	Br. pp
164	Indigo	Od. of HCN, alk. vap. brns.	—	V. sl.	Insol.	Nil	Nil	Nil	Nil
165	Indigo Carmine	Ch. and gives off water	—	100	Insol.	Deep bl. ppt.	Col. dis- char- ged slow- ly	Nil	Dk. gr. ppt
166	Iodoform	M., vi. vap.	120 -122	V. sl.	100	Nil	Nil	Nil	Nil
167	Iodophtha- lein	Ch., iodine vap.	—	7	Sl.	Nil	Br. ppt.	Nil	Nil
168	Iodopyr- role	Bl. sub. c. vi. vap.	De- comp. above 140	V. sl.	21	Nil	Nil	Nil	V. s. ppt
169	Lactose	M., ch., od. of burnt sugar	—	7	Insol.	Nil	Nil	Nil	Nil
170	Lævulose	M. to br. liq. c. caramel od. and ch., vap. brns.	About 95 when an- hyd.	Less than 0.5	About 16	Nil	Nil	Nil	Nil
171	Lecithin (Ovo-)	M. c. character- istic od.	—	Sl.	30 misc. c. 1, but throws out c. more	Nil	Nil	Nil	Or. br. pp
172	Lithium Acetyl- salicylate	M., ch., od. of phenol and sali- cylic esters	—	1	4	Nil	Nil	Nil	Yel. pp

BROM. AQ.	SPECIAL TESTS.
Yell. ppt. rediss. at first	Gives reactions of chloral and phenazone. Gives green ppt. with NaNO_2 and HCl .
Nil	Purple vapours on heating in test-tube. Colour disappears on treatment with alkaline reducing agents, <i>e.g.</i> , NaOH and Zn .
Dark gr. ppt. dissolv- ing to br. sol.	Ash contains sodium sulphate. Diazo Test gives green colour. Colour of aq. sol. destroyed by HNO_3 or bromine wtr., or by Zn and NaOH .
Nil	Iodine is pptd. on adding nitric acid to a solution in warm alcoholic potassium hydroxide.
Yell. ppt.	Cream ppt. c. HCl wh. rediss. in excess of NaOH c. return of bl. col. which subsequently disappears. Fused c. NaOH , diss. in HNO_3 and treated c. AgNO_3 —yell. ppt.
Nil	Warmed c. NaOH and Zn fumes of pyrrole are given off and colour pine wood (<i>e.g.</i> , a match) soaked in HCl red. Alc. sol. c. HNO_3 gives red col.
Nil	Reduces Fehling's solution on heating. Becomes brown on heating with alkalis.
Nil	Reduces bismuth salts in alkaline solution. On warming with KOH or NaOH turns brown (as also dextrose). Fermentable directly but more slowly than dextrose. Combines with calcium hydroxide, forming insoluble gelatinous salt. Specific rotation of well-boiled 10% aq. sol. about -93° if pure.
Dilute emul- sion gives orange ppt.	Characteristic waxy appearance. Boiled with baryta gives glycerophosphoric acid, neurine, and a fatty acid (stearic, oleic or palmitic).—Watts.
Wh. ppt.	HCl ppts. aspirin; filtrate give reactions for Li . After hydrolysis gives reactions for salicylic acid.

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in-)	SOL. ALC. (1 in-)	MAY- ER'S	GOLD CHL.	ACID PIC- RIC.	DRA
	Luminal (see Pheno- barbitone)								
173	Magnesium Acetyl- salicylate	M., ch., od. of phenol and acetic acid	—	12	Insol.	Nil	Nil	Nil	Yell ppt.
174	Malachite Green	Part m., goes gr. up tube and then br. vap. brns.	—	2	About 30	Dk. gr. ppt.	Dk. gr. ppt.	Dk. gr. ppt.	Dk. dirty br. ppt.
175	Mannitol Nitrate	M., goes br. and explodes	113	Al- most insol.	Sl.	Nil	Nil	Nil	Nil
	Medinal (see Bar- bitone, Soluble)								
176	Mercurio- chrome	Chars.	—	Read- ily	Insol.	Nil	Pur- ple col.	Nil	Red ppt.
177	Mercury Succini- mide	Ch., grey sub., vap. brns., sl. cyanide od.	—	28	V. sl.	Yell. ppt. turns or.	Nil	Nil	Br. ppt. turn crm
178	Methylacet- anilide	M. and sub.	100 -101	60	Read- ily	Nil	Nil	Nil	Br. ppt.
179	Methyl- Asprio- dine	M., distils c. sl. decomp.	40	Insol.	Misc.	Nil	Nil	Nil	Nil
180	Methylene Blue	Swells and ch., sulphur od.	—	About 6	Sl.	Bl. ppt.	Blk. ppt.	Red ppt.	Blk ppt.
181	Methylene Ditannin	Ch. c. br. dist., tannin od.	220 -240 c. de- comp.	Insol.	About 3	Nil	Vi. col.	Nil	Ni

O.	BROM. · Aq.	SPECIAL TESTS.
3	Wh. ppt.	HCl precipitates aspirin; filtrate gives reactions for Mg. After hydrolysis gives reactions for salicylic acid.
4	Dark gr. ppt.	Its solubility in amyl alcohol distinguishes it from methyl green and its allies. Aq. sol. becomes red on acidifying c. HCl. Colour base is pptd. on addition of NaOH and when recryst. from benzene has m.p. of about 132°.
5	Nil	Explodes at 120°.
6	Col. discharged	HCl precipitates dibromohydroxymercurifluorescein. Heated c. H ₂ SO ₄ and HNO ₃ , cooled and diluted c. water gives a ppt. of HgS c. H ₂ S. Fused c. NaOH and dissolved in dil. HNO ₃ , gives a ppt. of AgBr c. AgNO ₃ .
7	Nil	Heated with alkali evolves ammonia.
8	Wh. ppt.	Hydrolysed to acetic acid and monomethylaniline. Soluble 1 in 2 of chloroform (distinction from acetanilide and phenacetin).
9	—	Fused c. NaOH and dissolved in dil. HNO ₃ , gives ppt. of AgI c. AgNO ₃ . Heated c. conc. H ₂ SO ₄ gives off vap. of iodine. Heated c. NaOH and acetic acid added, sol. gives vi. col. c. FeCl ₃ .
0	Blk. ppt. and sol. almost colourless	Aq. sol. decolourised on warming c. Zn dust and acetic acid, col. reappearing if sol. is filtered and exposed to air. Aq. sol. c. KI sol. gives deep blue flocculent ppt. Aq. sol. c. sl. acid sol. K ₂ Cr ₂ O ₇ gives bl.-vi. ppt., the liquid becoming red-vi. but the bl. is restored c. H ₂ SO ₃ . HNO ₂ converts to methylene green.
1	Nil	0.1 g. heated with 2 ml. conc. H ₂ SO ₄ gives a br. col. changing to gr. and then bl., and on adding alcohol a bl. turning to wine-red.

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in-)	SOL. ALC. (1 in-)	MAY- ER'S.	GOLD CHL.	ACID PIC- RIC.	DRAG.
182	Methyl- sulphonal	M., boils, ch., c. od. of SO ₂ and mercaptan	76 -78	320	12	Nil	Nil	Nil	Nil
	Migraine (see Phenaz- one and Caffeine Citrate)								
183	Morphine	M., ch., br. dist. alk. vap. brns.	About 230°, de- comp.	5000	100	Nil	Op- ales- cence	Nil	Red- br. ppt.
184	Morphine Hydrochlor.	Ch. c. br. dist.	—	25	About 50	Yell.- wh. gela- tin- ous ppt.	Yell.- br. ppt. turns dar- ker	Yell. ppt.	Red- br. ppt.
185	Nicotine	Evaps. c.. naus. od.	—	Misc.	Misc.	Wh. ppt.	Buff ppt.	Yell. ppt.	Br. ppt.
186	Nitro- benzene	Dist., ch. sl., vap. brns.	—	Sl.	1	Nil	Nil	Nil	Light br. ppt.
	Novocain (see Pro- caine Hydro- chlor).								
187	Nuclein	Ch., br. alk. vap. brns.	—	V. sl.	Insol.	Nil	Nil	Nil	Nil
188	Orthocaine	M. to yell. liq., ch., br. dist. and alk. vap. brns.	141- 143	Sl.	7	Nil	Dk. gr. ppt.	Nil	V. sl. red- br. ppt. slow- ly
189	Papa- verine	Alk. fishy vap.	146 -147	Insol.	V. sl.	Wh. ppt.	Buff ppt.	Yell. ppt.	Br. ppt.

No.	BROM. AQ.	SPECIAL TESTS.
82	Nil	Heated c. anhydrous sodium acetate, H_2S is evolved. Heated c. charcoal gives od. of mercaptan.
83	Nil	Sprinkled on to HNO_3 gives or.-red colour. Heated c. H_2SO_4 on a water-bath for 15 mins., cooled and treated c. HNO_3 gives blood-red colour. Froehde's Reagent gives reddish-vi., changing to slate blue. Liberates iodine from iodic acid. Gives blue ppt. c. $FeCl_3$ and $K_3FeC_6N_6$ sol. (freshly prepared).
84	Nil	Gives reactions of morphine and hydrochloride.
85	Yell. ppt. rediss. at first	Liquid, strongly alk. Dropped on paper, causes a grease spot, which disappears after a time. Phosphomolybdic acid gives greenish ppt. Platin. chlor. and tannin also ppt. in dilutions of 1 in 5000 and 1 in 500 resp. Treated with a drop of formaldehyde sol. and then HNO_3 —rose red col.
86	Nil	Detection of traces: distil with a little sulphuric acid in steam, shake distillate with chloroform, convert oily drops into aniline by reduction with zinc and sulphuric acid.
87	Nil	<i>Cf.</i> Acid Nucleinic.
88	Dirty gr.-br. ppt.	5% aq. sol. c. 10% aq. sol. $NaNO_2$ acidified c. HCl gives yell.-wh. and on exposure to air an or. ppt. darkening to red. Distinguished from amydracaine, amylocaine, benzamine, cocaine, holocaine, procaine and tropacocaine by Froehde's Reagent which gives a faint vi. tinge but nil c. others except tropacocaine which gives slight gr. Gives no ppt. c. sol. I (distinction from benzocaine).
89	Yell. ppt.	0.01 g. c. 5 ml. H_2SO_4 gives colourless sol. becoming rose-red at 110° and darkening to vi. at 200° , the colour being discharged on adding wtr. Gives rose-red colour c. H_2SO_4 containing sol. of formaldehyde. Aq. sol. $K_3FeC_6N_6$ gives c. a faintly acid sol. a yell. ppt. which when washed and dried diss. in H_2SO_4 containing sol. of formaldehyde, giving a pale blue colour darkening to bl.-vi.

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in—)	SOL. ALC. (1 in—)	MAY- ER'S.	GOLD CHL.	ACID PIC- RIC.	DRAC
190	Parafor- malde- hyde	Part m. and sub. vap. brns.	Vola- tilises at 100	V. sl.	Sl.	Nil	Nil	Nil	Nil
191	Paralde- hyde	Evaps., vap. brns.	11— 12	9	Misc.	Nil	Nil	Nil	Nil
192	Pelletierine Tannate	M., ch., and alk. vap. brns.	Soft- ens at about 165° but de- comp. s. melt- ing	700	8	Nil	Nil	Yell. ppt.	Dk. br. ppt.
193	Phenacetin	M. and volatilises almost completely; vap. brns.	134— 136	Insol.	21	Nil	Nil	Nil	Nil
194	Phenalgin	Part m. and eff., dense sub., ch., alk. vap. brns.	—	Part	Part	Nil	Sl. dark ppt.	Nil	Nil
195	Phenazone	M. then ch. and br. vap. brns.	111 —113	1¼	1½	Wh. ppt.	Buff ppt.	Yell. ppt.	Red br. ppt.
196	Phenazone Acetyl- Salicylate	M., ace- tic then phenolic vap.	About 45	160	3½	Wh. ppt.	Yell. ppt.	Nil	Red ppt.
197	Phenazone and Caffeine Citrate or Salicy- late	M. then ch. and gives br. alk. vap. brns.	101 —105	2	1	Wh. ppt.	Dull yell. ppt.	Yell. ppt.	Or. red ppt.

No.	BROM. AQ.	SPECIAL TESTS.
90	Nil	Formalin odour on heating. Distillate in water reduces silver nitrate (forming mirror). Responds to Schiff's Test (sulphurous fuchsin solution). Na nitroprusside, 0.5%, gives red, which on acidifying c. acetic acid changes to purple. Nessler's reagent gives a reddish precipitate which gradually changes to grey. If to 5 ml. H_2SO_4 in which 0.02 g. salicylic acid is dissolved, 2 drops of formalin (37%) be added and the liquid gently warmed, a permanent red col. forms (U.S.P.). In general, gives the reactions of aldehydes.
91	Nil	More soluble in cold water than hot—sat. aq. sol. becomes turbid on warming. Gives mirror with ammoniacal silver nitrate on warming. Gives reactions of aldehydes, but does not add ammonia or sodium bisulphite. Warmed c. H_2SO_4 it is converted into acetaldehyde.
92	Wh. ppt.	Gives deep blue ppt. with cobalt or copper sulphate. The base absorbs oxygen from the air, resinifying. Pelletierine with sulphuric or selenious acid gives a red col., deepening on heating and changing to green (distinction from arecoline).
93	Nil	$K_2Cr_2O_7$ in HCl sol. gives red col. 1 ml. of a sol. of 0.2 g. in 2 ml. HCl (25%) boiled, cooled and filtered gives reddish violet on adding 5 drops Cl water, and vi. changing to red on adding 1 drop $K_2Cr_2O_7$ sol. Colour reaction (Carletti): moisten a small quantity of phenacetin in a dish c. acetaldehyde, and 2 to 3 ml. H_2SO_4 ; on stirring with a rod the acid turns red (increased by warming). Sensitive to 0.001 g.
94	Wh. ppt. and eff.	Alcoholic extractive evaporated to dryness gives reactions of acetanilide. Also contains sodium bicarbonate and ammonium carbonate.
95	Yell. ppt. rediss.	Aq. sol. c. trace $NaNO_2$ and dil. H_2SO_4 gives gr. col. 1 to 2 ml. of 0.1% aq. sol. c. 1 drop $FeCl_3$ sol. gives deep red col. changed to light yell. by dil. H_2SO_4 . Aq. sol. gives c. eq. vol. HNO_3 yell. sol. changing to crimson on warming. Tannin gives a white ppt. c. 1% sol.
96	Wh. ppt.	Gives reactions of phenazone and acetylsalicylic acid.
97	Yell. ppt. rediss.	Gives reactions of phenazone and caffeine. Citrate radicle is not pptd. by $CaCl_2$. Salicylic acid is extracted by ether from aq. sol. acidified c. HCl. Caffeine may be detected by murexide test if all phenazone pptd. by Br water is filtered off.

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in-)	SOL. ALC. (1 in-)	MAY- ER'S	GOLD CHL.	ACID PIC- RIC.	DRA
198	Phenazone Salicylate	M., ch., br. dist., alk. vap.	90	240	4	Wh. ppt.	Sl. buff ppt.	V. sl. yell. ppt.	Rec. br. ppt.
199	Phenobar- bitone	Ac. vap., sweet od.	173- 177	V. sl.	15	Nil	Nil	Nil	Nil
200	Phenobar- bitone, Soluble	Ac. vap., sweet od.	—	Read- ily	Read- ily	Nil	Nil	Nil	Or. ppt.
201	Phenocoll Hydrochlor.	Part m. and ch., br. sub., alk. vap.	—	16	34	Wh. ppt.	Nil	Yell. ppt. bec. cryst.	Br.- red ppt.
202	Phenocoll Salicylate	M. to br. liq., ch., alk. vap.	160- 165 de- comp.	Sl.	50	Nil	Nil	Yell. crys- tals form slow- ly	Br.- red ppt.
203	Phenol	M. and evaps., vap. brns.	39- 40	12	0·16	Nil	Blk. ppt. comes v. slow	Nil	Nil
204	Phenolph- thaleïn	M. to br. liq., ch., c. phenol od.	254- 258	Insol.	10	Nil	Nil	Nil	Nil
205	Phenyl- Asprio- dine	M., boils, ch., iodine vap. c. phe- nol od.	123	Insol.	250	Nil	Nil	Nil	Nil
206	Phenyl- hydrazine Hydrochlor.	M., boils, sublimes, then ch. c. aniline od.	—	Sol.	Sol.	Nil	Blk. ppt.	Nil	Br.- blk ppt.
207	Phenyl- Sedasprin	M., boils, ch. c. HBr and irrit. salicylic ac. od.	118	Insol.	380	Nil	Nil	Nil	Nil

D.	BROM. AQ.	SPECIAL TESTS.
8	Wh. ppt.	Gives reactions of phenazone and salicylic acid.
9	Nil	<p><i>To distinguish from barbitone.</i> Diss. 0.1 g. in 1 ml. H_2SO_4 and add trace NaNO_2—or. col. c. phenobarbitone, none c. barbitone. Heat c. NaOH, acidify c. H_2SO_4—CO_2 evolved c. sweet acetic od. Gives ppt. c. Millon's Reagent c. or s. HNO_3. Mix 0.1 g. c. 0.5 g. KNO_3 and 2 ml. H_2SO_4. Heat on boiling water-bath 10 mins. and pour into 10 ml. cold wtr. Reduce pptd. nitro-compd. c. Zn, and decant sol. Cool, acidify, add aq. sol. of 0.1 g. KNO_2 and add to a sol. of β-naphthol in NaOH—blood-red col. distinguishes barbituric acid c. phenyl group.—<i>J. Pharm. Chim., Paris</i>, 1925, 117, 69, per <i>Analyst</i>, 1925, 465.</p>
0	Wh. ppt.	Gives reactions of sodium and yields ppt. of phenobarbitone on acidifying the aqueous solution.
1	Yell. ppt. rediss. at first	On treating 1 ml. of sol. of 0.2 g. in 2 ml. of HCl (25%), boiled, cooled and filtered, with 5 drops of fresh Cl water, gives reddish-vi. colour. 0.1 g. boiled with 2 ml. 33% NaOH and then 2 drops of CHCl_3 added gives phenyl isocyanide odour and blk. drops on surface.
2	Wh. ppt.	Reactions of phenocoll and salicylic acid.
3	Wh. ppt. rediss. at first	To 0.001 g. in 10 ml. water add 1 drop of 10% sod. nitrite sol. and pour on to H_2SO_4 . A coloured zone—red above, green below—appears at the junction. Bleaching powder to aq. sol. gives violet colour.
4	Nil	Red colour with caustic alkalis disappearing with acids. Silver nitrate gives a violet ppt.
5	—	Fuse c. soda-lime, dissolve in aq., acidify c. HNO_3 and add AgNO_3 —yell. ppt.
6	Yell. ppt. with excess	Reduces Fehling's solution in cold. 1 in 50,000 stated to be detected by following test:—To sol. add a few drops of aqueous trimethylamine and several drops of sodium nitroprusside. A bl.-gr. colour is produced, bec. more marked on addition of KOH and red if heated after.
7	—	Fuse c. soda-lime, dissolve in aq., add HNO_3 and AgNO_3 —yell. ppt. Boil c. NaOH , cool, add ac. acetic and FeCl_3 . Violet col. produced.

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in-)	SOL. ALC. (1 in-)	MAY- ER'S.	GOLD CHL.	ACID PIC- RIC.	DRAG
208	Phloridzin	M. c. sl. eff., ch., br. dist. and vap. brns.	107 solidifies and again m. 170	V. sl.	4½	Nil	Nil	Nil	Nil
209	Physostigmine	M., ch., v. irrita- ting alk. vap. brns.	105 -106	Sl.	2	Wh. ppt.	Br. ppt. and purplish sol.	Yell. ppt.	Red ppt.
210	Physostigmine Salicylate	M., c. irritating alk. vap. brns.	140	Less than 1	Less than 2	Wh. ppt.	Fawn ppt. turn- ing to blk. c. purple sol.	Yell. ppt.	Red- br. ppt. turn- ing or.
211	Picrotoxin	M., ch., br. dist.	About 200	Sl.	13½	Nil	Nil	Nil	Nil
212	Pilocarpine Nitrate	Ch., alk. vap.	174 -178	9	50	Wh. ppt.	Crm. yell. ppt.	Yell. ppt.	Br.- red ppt.
213	Piperazine	M. and evaps., vap. brns.	43 -44 108- 110 when anhyd.	2	3	Sl. wh. ppt.	Red- br. ppt.	Sl. yell. ppt.	Blk. to yell. ppt.
214	Piperazine Benzoate	M. and evaps., vap. brns.	About 167	100	10	Nil	V. sl. buff ppt.	Yell. ppt.	Red. br. ppt.
215	Piperidine Tartrate	M., vap. c. celery od.	About 80	Less than 1	About 30	Wh. cryst. form	Nil	Nil	Br. ppt.
216	Podophyllo- toxin	Part m., ch., br. dist. and vap. brns.	117	V. sl.	Misc.	Nil	Nil	Nil	Nil

No.	BROM. AQ.	SPECIAL TESTS.
08	Sl. yell. ppt.	Sols. have avidity for AmOH. In taking up 10% it turns red and melts to a colourless mass. Mix 0.1 g. with a crystal of vanillin and 1 drop of HCl and warm—red col.
09	Yell. ppt.	See under physostigmine salicylate.
10	Yell. ppt. re- diss. at first	Warmed c. few drops AmOH a yellowish-red col. is produced, and on evaporation a bl. residue giving a bl. alc. sol. On adding acetic acid the sol. is bl. by transmitted light c. a red fluorescence intensified on dilution c. wtr.
11	Nil	Mixed c. thrice its weight of KNO_3 , moistened c. H_2SO_4 and then NaOH in excess added gives red.—Langley's Reaction. On the addition of 1 drop 20% anisaldehyde in dehyd. alc. to a trace of picrotoxin moistened c. H_2SO_4 , a vi. col. is produced (Melzer).
12	ppt. rediss. at first	To 2 to 3 ml. of 0.2% aq. sol. acidified c. 1 or 2 drops dil. H_2SO_4 add eq. vol. sol. H_2O_2 and pour layer of benzene on to the mixture; add 1 or 2 drops of sol. $\text{K}_2\text{Cr}_2\text{O}_7$ and shake. Benzene layer becomes coloured bl.-vi., the aqueous layer remaining yellow (distinction from other alkaloids).
13	Yell. ppt. re- diss. at first	Dissolves uric acid forming the neutral urate. Gives white ppt with Nessler's Reagent. Piperazine phosphate forms 4-sided tabular crystals.
14	Yell. ppt. re- diss. at first	HCl to aq. sol. gives ppt. of benzoic acid. The aq. sol. gives test for piperazine <i>q.v.</i>
15	Yell. ppt.	Piperidine is a liquid with ammoniacal and peppery odour, and is a very strong base.
16	Nil	Alkalis convert into gelatinous acid which loses water, giving a substance melting at 227° .

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in—)	SOL. ALC. (1 in—)	MAY- ER'S.	GOLD CHL.	ACID PIC- RIC.	DRA
217	Potassium Antimonyl- tartrate	Blackens, grey-wh. sub.	—	17	Insol.	Nil	Nil	Nil	De- color- ises
218	Potassium Hydroxy- quinoline Sulphate	M. c. eff.	Partly lique- fies at 172	1	Sl.	Crm. ppt.	Buff ppt.	Yell. ppt.	Red- br. to blk.
219	Procaine Hydrochlor.	M. to clear liq., ch. c. alk. vap. and nauseous od.	154– 156	1	8	Wh. ppt.	Br. ppt.	Yell. ppt.	Red- br. ppt.
220	Proflavine	Alk. vap. containing H ₂ S	—	300	48	Or. ppt.	Deep gr. fluor.	Or. ppt.	Br. ppt.
221	Proponal	Distils	145	Insol.	Sl.	Nil	Nil	Nil	Nil
	Pyramidon (see Amido- pyrine)								
222	Pyrogallol	Sub. c. decomp.	129 –135	2	1	Nil	Re- duc- tion	Nil	Nil
223	Quinidine	M., ch., br. vap. and distillate	About 168	Pract. insol.	17	V. sl. ppt.	V. sl. ppt.	V. sl. ppt.	V. sl. ppt.
224	Quinidine sulphate	M. to red. liq., ch. c. vi. vap.	About 200 –202 de- comp.	90	10	Wh. ppt.	Buff ppt.	Yell. ppt.	Brick red ppt.
225	Quinine	M., ch. c. br. dist. and alk. vap. brns.	About 174 when anhyd.	V. sl.	1	Wh. ppt.	Crm. ppt.	Yell. ppt.	Br.- red ppt.

	BROM. AQ.	SPECIAL TESTS.
7	Nil	0.00005 g. in 5 ml. wtr. made acid gives or. col. c. H_2S . Larger amount gives ppt. soluble in ammon. sulphide or KOH. With Marsh Test—black mirror insol. in sod. hypochlor. sol. With lime water—wh. ppt. soluble, when freshly pptd., in acetic acid and ammon. chloride.
8	Yell. ppt.	Diazo test gives sl. br.-red. Aq. sol. c. $FeCl_3$ gives bright gr. colour. Bromine wtr. gives ppt. of dibromohydroxyquinoline. Gives ppt. c. salts of some metals (see this Vol., p. 217).
9	Yell. ppt. rediss., finally wh. ppt.	Anhydrous base recryst. from light petroleum has m.p. of 58° to 60° . Aq. sol. c. trace $NaNO_2$ and HCl, added to sol. β -naphthol in dil. NaOH gives scarlet ppt. Slightly acid sol. immed. decolorises sol. $KMnO_4$ (distinction from cocaine). Aq. sol. c. aq. sols. $NaNO_2$ and Na_2CO_3 containing 0.5% potass. guiacolsulphonate and acidifying c. HCl, a red to yell. col. is prod. varying with the concentration.— <i>J. chem. Soc. Abstr.</i> , ii/1925, 247.
0	Buff ppt.	Sols. are similar to those of acriflavine. SO_4 reactions. Aq. sol. reduces permanganate readily and gives ppt. c. sol. of formaldehyde.
1	Nil	After heating c. NaOH and acidifying c. H_2SO_4 , CO_2 evolved—pungent vapour c. odour resembling menthol. Sat. sol. gives white ppt. with Millon's. No colour with Nessler's Reagent except on fusing with KOH.
2	Nil	In presence of alkali it rapidly absorbs oxygen, giving a dark-coloured solution.
3	Nil	Slightly acid sol. treated c. bromine and then ammonia gives green coloration.
4	Yell. ppt.	Gives a wh. ppt. gradually on adding silver nitrate sol. to sat. sol.
5	Yell. ppt.	Dissolves c. blue fluorescence in H_2SO_4 , acetic acid or tartaric acid. White ppt. c. AmOH soluble in ether and in excess of AmOH. 1 ml. of 1% quinine (diss. c. dil. H_2SO_4) c. 2 to 3 ml. bromine wtr. followed by 1 ml. dilute sol. of ammonia gives emerald-green colour (Thalleioquinin Test). Is distinctive for quinine and shows less than 0.0001 g. Belladonna, colchicum, conium, gelsemium, ipecacuanha, opium, nux vomica do not inhibit the reaction. Use dilute sols.

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in—)	SOL. ALC. (1 in—)	MAY- ER'S	GOLD CHL.	ACID PIC- RIC.	DRA
226	Quinine Ethyl Carbonate	M., ch., yell. vap. c. sweet od.	About 90– 92 when dried	Sl.	2	V. sl. ppt.	V. sl. ppt.	V. sl. ppt.	Nil
227	Quinine Sulphate	M. to red liq., ch. c. vi. then br. vap.	—	800	100	Wh. ppt.	Crm. ppt.	Yell. ppt.	Br- red ppt.
228	Quinoline	Evaps. and vap. brns.	—	Sl.	Misc.	Wh. ppt.	Crm. ppt.	Yell. ppt.	Red br. to blk. ppt.
229	Resorcinol	M. & sub., vap. brns. c. sweet od.	110	1	0·5	Nil	Grad. goes gr.	Nil	Nil
230	Resorcinol Mono- acetate	Bright red near edge of liq., acetic od., vap. brns. and ch.	—	Sl.	Misc.	Nil	Bl. str'ks come v. sl'wly	Nil	Red br. ppt.
231	Saccharin	M. to clear liq., ch., wh. cryst. sub. and vap. brns. c. arom. od.	About 225	Sl.	38	Nil	Nil	Nil	Nil
232	Saccharin Soluble	M., ch., yell. vap. c. arom. od.	—	1·5 at 25°	50 at 25°	Nil	Nil	Nil	Nil
233	Salacetol	M. and ch., vap. brns.	67	Sl.	14	Nil	Nil	Nil	Nil
234	Salicin	M. then ch., c. caramel od.	199– 201	28	80	Sl. opal.	Nil	Nil	Nil

O.	BROM. AQ.	SPECIAL TESTS.
6	Nil	Solutions in dil. acid give reactions of quinine. On warming c. NaOH and iodine sol., iodoform is pptd.
7	Yell. ppt. re- diss. at first	<i>See</i> reactions for quinine.
8	Yell. ppt.	B.p. 236° to 238°. Reacts c. methyl iodide forming a methiodide, m.p. 134°. The amorphous ppt. c. Mayer's reagent forms characteristic yell. needles on adding HCl.—Allen.
9	Yell. ppt. re- diss. at first	On heating 0.05 g. with 0.1 g. tartaric acid and 10 drops conc. H ₂ SO ₄ , carmine liquid forms which is yellow on diluting c. wtr. Not pptd. by neutral lead acetate (distinction from pyrocatechin). Bluish violet with FeCl ₃ changing to yellow on adding AmOH; distinction from catechol and quinol.— <i>U.S.P. X.</i> Resorcinol and phloroglucinol are the only ordinary phenolic compds. giving coloured ppt. immed. in the cold when 2 ml. of 40% formaldehyde and 3 ml. conc. HCl are added to a sol. of 0.1 g. in 3 ml. 95% alcohol.— <i>J. chem. Soc. Abstr.</i> , i/1924, 638.
0	Yell. ppt. re- diss. at first	Gives reactions of resorcinol and acetic acid.
1	Nil	Dissolved in 25% KOH, <i>q.s.</i> , and bromine water added until yell., bromine substitution body is thrown out. 0.0001 g. heated c. 1 mg. resorcinol and 1 drop H ₂ SO ₄ gives yell. then dark green. After cooling dissolve in wtr. and add 1 or 2 drops 33% NaOH—intense fluorescence.
2	Nil	Gives reactions of saccharin and leaves residue of sodium sulphate on ignition.
3	Wh. ppt.	Gives on alkaline hydrolysis reactions of salicylic acid, and the liquid reduces Fehling's, smells of meth. salicyl. and burnt sugar, and turns yell.
4	Nil	Heated c. K ₂ Cr ₂ O ₇ and dil. H ₂ SO ₄ gives salicylic aldehyde (meadowsweet). Dissolves in HCl, and on boiling throws out resin (saliretin). Gives blood-red col. c. conc. H ₂ SO ₄ .

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in—)	SOL. ALC. (1 in—)	MAY- ER'S.	GOLD CHL.	ACID PIC- RIC.	DRA
235	Salicyl Salicylate	M., wh. sub., ch. c. phenol od., vap. brns.	142	Very sl.	15	Nil	Nil	Nil	Nil
236	Sal Limonis (Potassium Quadroxalate)	Ch. and sl. vap.	—	About 40	Sl.	Nil	Nil	Nil	Br. ppt.
237	Salol	M., boils c. phenol od.	42— 43·5	V. sl.	15	Nil	Nil	Nil	Nil
238	Santalyl Salicylate	Part evaps.	—	Insol.	Sl.	Nil	Nil	Nil	Nil
239	Santonin	M. to clear liq., ch., gives br. dist.	171 —174	V. sl.	44	Nil	Nil	Nil	Nil
240	Sedasprin	M., ch. c. pungent od.	136	1500	4	Nil	Nil	Nil	Nil
241	Silver Lactate	Ch., vap. brns.	—	18	500	Yell. ppt.	Light br. ppt.	Sl. ppt.	Br. ppt. bec. wh.
242	Silver Proteinate	Swells ch., alk. vap. brns.	—	Read- ily	V. sl.	Col. dis- charged	Col. prt'ly dis- charged	Br. ppt.	Br. ppt. bec. wh.
243	Silver Proteinate Mild	Swells, ch. alk. vap. brns.	—	Read- ily	Insol.	Nil	Pple- blk. ppt.	Br. ppt.	Yell. ppt. col. dis- charged
244	Sodium Aminar- sonate	Ch., blk. sub. and alk. vap.	—	5	125	Nil	Br. col.	Nil	Br. ppt.
245	Sodium Cacodyl.	M., sub., inflam. c. garlic od.	About 60	0·5	1	Nil	Sl. buff ppt.	Nil	Red br. ppt.
246	Sodium Glyceroph.	Ch., irrit. vap. brns.	—	4	Sl.	Nil	Nil	Nil	Nil

No.	BROM. AQ.	SPECIAL TESTS.
35	Sl. yell. ppt.	Yields salicylic acid on hydrolysis.
36	Nil	Calcium chloride gives white ppt. insoluble in acetic acid. Potash flame. Decolorises KMnO_4 with effervescence on warming at 60° to 65° with dil. H_2SO_4 .
37	Nil	Alc. sol. ppts. c. bromine. Violet c. FeCl_3 in alc. sol. Test for phenol and salicylic acid after heating c. alc. KOH.
38	Nil	Alcoholic solution coloured violet by FeCl_3 .
39	Nil	Warmed on w.b. c. 50% H_2SO_4 and a trace of FeCl_3 , yell. col. forms, changing through red to vi., or a blood-red can be extracted by amyl alc. A crystal warmed c. ethyl nit. sol. and a few drops of KOH gives a rose-red; with alc. KOH alone a vi.-red col. is obtained.
40	Nil	Hydrolyse c. HCl, neutralise c. NaOH, add FeCl_3 —violet colour. Fuse c. soda lime, dissolve and acidify c. HNO_3 , yell. ppt. c. AgNO_3 .
41	Wh. ppt.	Residue on ignition gives reactions for Ag.
42	Yell.- wh. ppt.	Sol. gives no ppt. c. ammon. sulphide but becomes blk.-br. To 2 ml. 5% aq. sol. add 1 drop acetic acid; a wh. ppt. is produced sol. in excess. 10 ml. 1% sol. c. 5 ml. NaOH becomes violet in a few minutes on adding 2 ml. 2% CuSO_4 sol.
43	Yell.- wh. ppt.	Contains about 20% Ag.
44	Wh. ppt.	0.001 g. in 5 ml. wtr. reduces KMnO_4 and gold chloride. FeSO_4 sol. gives olive-gr. ppt. Sod. hypobromite gives bluish-red colour.
45	Nil	Few drops of aq. sol. with 2 ml. hypophosphorous acid develops garlic odour of cacodyl in a short time. Aq. sol. with mercuric nitrate sol. gives wh. ppt. becoming yell.
46	Nil	Solid compd. is Na salt of β -glycerophosphoric acid. The salt of the α -acid occurs usually as a 50% sol. An aq. sol. of the former does not reduce cold periodic acid. On incineration pyrophosphate is formed. Lead acetate precipitates but not magnesia mixture. Cold ammonium molybdate precipitates either on standing or heating.

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in—)	SOL. ALC. (1 in—)	MAY- ER'S	GOLD CHL.	ACID PIC- RIC.	DRA
247	Sodium Phenol-sulphonate	Decrepi- tates, ch., vap. brns. c. phenol od.	—	6	150	Nil	Nil	Nil	Nil
248	Sodium Salicylate	Ch. c. od. of phenol	—	1		Nil	Nil	Nil	Nil
249	Sodium Sulpho-ricinate	Evaps., ch.	—	Misc.	Misc.	Nil	Nil	Nil	Yell. br. ppt.
250	Sodium Taurogly-cocholate	Part m., swells up, vap. brns.	—	0·5	About 2	Nil	Nil	Nil	Br. resin- ous ppt.
251	Sodium Tetrabro-mophenol-phthalein Sodium Tetraiodo-phenol-phthalein (see Iodo-phthalein)	Coke- like od. of bromo- phenol	—	Read- ily	Insol.	Nil	Pple -blue by refl. light	Crim- son	Or. ppt.
252	Sparteine Sulphate Stovaine (see Amylo- caine Hydrochlor.)	M., boils, ch., c. pyridine od., vap. brns.	150 when anhyd.	Less than 0·5	5	Wh. ppt.	Buff ppt.	Yell. ppt.	Red br. ppt.
253	Strophan-thin	Swells, ch. c. br. dist., vap. brns.	—	Less than 1	About 1	Nil	Nil	Nil	Nil
254	Strychnine	M. to br. liq. and vap. brns.	270 -280 c. de- comp.	V. sl.	150	Wh. ppt.	Buff ppt.	Yell. ppt.	Or br pp

BROM. AQ.	SPECIAL TESTS.
Decolo- rised	Dilute solution does not give yellowish brown with uranium nitrate solution (distinction from salicylate). Incineration gives about 30% Na_2SO_4 .
Wh. ppt.	See salicylic acid.
Yell. ppt.	Occurs as a stiff paste with characteristic odour.
Resin- ous greyish ppt.	Taurocholic acid forms shining hygroscopic bitter needles easily sol. in water and alcohol. Solutions dextrorotatory. On heating at 100° or boiling with KOH or acids, decomposes into cholic acid, $\text{C}_{24}\text{H}_{40}\text{O}_5$, taurine, $\text{C}_2\text{H}_7\text{NO}_3\text{S}$, and glycerin. To aq. sol. add a crystal of sucrose and conc. H_2SO_4 drop by drop; a br.-red. col. is produced changing through vi. to bl. on keeping.—Pettenkofer's Bile Acid Test.
Yell. ppt.	Fused c. NaOH, diss. in HNO_3 and treated c. AgNO_3 —yell. ppt. of AgBr. On acidifying aq. sol. light buff ppt. of the phthalein is produced.
Yell. ppt. re- diss. at first	White ppt. with CdI_2 . Sodium phosphomolybdate gives white ppt. soluble on heating. Ammon. sulphide forms or. col. To 0.1 g. add 25 ml. ether and a few drops AmOH followed by a 2% ethereal solution of iodine until the liquid acquires a dark red-br. col.; a gr.-br. cryst. ppt. forms on the sides of the bottle. Grant's Test.—A strip of filter ppr. moistened c. the chlorof. ext. of ammoniacal solution of the alkaloid is dried and is exposed to Br. then to NH_3 fumes. On finally warming, a bright pink colour forms.— <i>J. chem. Soc. Abstr.</i> , ii/1925, 448.
Nil	Strophanthin B.P. '32 is adjusted to standard activity by admixture with lactose. The m.p. and sol. of unadjusted substance vary with the method of extraction. Aq. sol. is dextro-rotatory. Dissolved in a cold mixture of H_2SO_4 , 4 vols., and H_2O 1 vol., an emerald-gr. col. is produced (distinction from ouabain).
Yell. ppt.	Trace diss. in H_2SO_4 and crystal of $\text{K}_2\text{Cr}_2\text{O}_7$ moved through sol. gives vi. col. passing through red to yell. Vitali's Reaction (see Atropine) gives yell. passing to vi. Mandelin's Reagent gives vi.-bl. changing to purple, and becoming red on dilution c. wtr. Phosphomolybdic acid will show 0.0001 g. picric acid 0.00005 g., tannic acid 0.00004 g., mercuric potassium iodide 0.000006 g., potassium bismuth iodide 0.00002 g., platonic chloride only 0.001 g. and gold chloride 0.0001 g.—Dragendorff.

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in—)	SOL. ALC. (1 in—)	MAY- ER'S	GOLD CHL.	ACID PIC- RIC.	DR
255	Strychnine Hydrochlor.	M. to br. liq., br. dist.	—	40	80	Wh. ppt.	Buff ppt.	Yell. ppt.	R p
256	Sucrose (Cane Sugar)	M. to yell. liq., ch. and vap. brns.	About 160. Does not re- cryst. on cool- ing	0·5	About 60	Nil	Nil	Nil	N
257	Sulphonal	Part m., cryst. sub., gar- lic vap.	125 –127	Sl.	80	Nil	Nil	Nil	N
258	Terpineol (Distillate from Ter- pinol)	Evaps. entirely, vap. brns.	—	Sl.	Misc.	Nil	Nil	Nil	B pp
259	Terpin Hydrate	M. evaps., inflam. sub.	116 –119	Sl.	14	Nil	Nil	Nil	N
260	Theobro- mine	M., sub., res. ch.	Sub. at 290 s. de- comp.	V. sl.	V. sl.	Nil	Nil	Nil	S re b p
261	Theobro- mine and Sodium Acetate	Part m., wh. sub., ch., alk. vap.	—	2	200	Nil	Nil	Nil	Ye b p
262	Theobro- mine and Sodium Salicylate	Ch. c. phenol od., wh. dist., vap.	—	1	Insol.	Nil	Br. col. and v. sl. ppt.	Nil	D b p b lig en
263	Theophyl- line	M. to yell. liq., sub., res. ch., vap.	265– 270	160	100	Nil	Nil	Nil	B b p
264	Theophyl- line and Sodium Acetate	Part m. and ch., vap.	—	25	Insol.	Nil	Br. col.	Nil	D b p
265	Thioresor- cinol	Ch., yell. sub. and vap.	—	V. sl.	V. sl.	Nil	Nil	Nil	N

BROM. AQ.	SPECIAL TESTS.
Yell. ppt.	Gives reactions of strychnine and of hydrochloride.
Nil	<p>Becomes brown when heated c. conc. KOH (Dextrose becomes brown in the COLD). Not directly fermentable—requires inversion by yeast or dilute acids. Does not form osazone or reduce Fehling's until hydrolysed.</p> <p>When a mixture of 1 ml. of saturated nickel ammon. sulph. sol., 1 ml. of sucrose sol. and few drops of H_2SO_4 or HCl is boiled the green colour changes to yellow and then to red. 0.005 g. of sucrose responds, other sugars not interfering.</p> <p>Sucrose can be separated from a dry mixture with dextrose by extraction with hot ethyl acetate, sucrose being insoluble.</p>
Nil	Fused c. KOH it becomes yell. then red, and on diluting c. wtr. blue. On acidifying a transient vi. is produced and S pptd. Heated c. charcoal, mercaptan is evolved.
Nil	Strong odour of hyacinths and lilac. B.p. 215° to 218° .
Nil	On adding few drops conc. H_2SO_4 to hot solution the liquid becomes turbid and odour of lilac is produced.
Nil	<p>Gives murexide reaction (<i>see under Caffeine</i>).</p> <p>Ppts. silver theobromine on adding $AgNO_3$ sol. to a very dilute sol. acidified c. HNO_3. On adding Br wtr. to sol. in HCl, boiling off Br, and adding trace $FeSO_4$ and few drops AmOH, a purple colour is produced.</p>
Nil	Gives Murexide Reaction. Aqueous solution 1 in 5 neutralised with dilute hydrochloric acid in presence of litmus solution gives white ppt. of theobromine. (A little alkali assists its solubility in water).
Wh. ppt., rediss. at first	On neutralising aq. sol. c. HCl, theobromine is pptd. On acidifying c. acetic acid and adding $FeCl_3$, a purple col. is produced.
Cryst. ppt. Nil at first	Gives Murexide Reaction. Distinguished from theobromine by giving a clear 4% sol. in AmOH.
Red-br. c. excess reagent	Gives reactions of theophylline and also of acetate (after removing the theophylline by neutralising and filtering).
Nil	Yellow powder. Oxidation gives a sulphonic acid.

No.	SUBSTANCE.	HEAT.	M.p. °C.	SOL. AQ. (1 in—)	SOL. ALC. (1 in—)	MAY- ER'S	GOLD CHL.	ACID PIC- RIC.	DRA
266	Thiosina- mine	M. c. garlic od., ch., alk. vap.	72— 74	17	2	Wh. ppt.	Buff ppt. re- diss.	Nil at first sl. ppt. after	Or. yell. ppt.
267	Thiosina- mine Ethyl Iodide	Ch., alk. vap. c. garlic od.	About 70	10	1	Wh. ppt.	Br.- blk. ppt.	Yell. ppt.	Red br. ppt.
268	Thymol	M., evaps., aromatic vap.	48— 51	About 1000	1	Nil	Nil	Nil	Nil
269	Thymol Iodide	Decomp. c. vap. of iodine	—	Insol.	Insol.	Nil	Nil	Nil	Nil
270	Tribromo- phenol	M., ch., wh. sub. c. irri- tating vap.	90— 95	Insol.	3	Nil	Nil	Nil	Nil
271	Trinitro- phenol	Burns, explodes if heated rapidly	121— 123	About 90	About 10	Nil	Nil	Nil	Nil
272	Tropaco- caine HCl	M., ch., br. sub.	About 271	2	About 9	Wh. ppt.	Yell. ppt.	Yell. ppt.	Red ppt.
273	Urea	M., gives wh. sub., and vap., res. solid. then sub.	130— 132	1	5	Nil	Nil	Nil	Nil
274	Urethane	M., evaps., vap.	47·5 —50	2	1	Nil	Nil	Nil	Nil
275	Veratrine	M. to yell.-br. liq., br. dist., vap.	145— 155	V. sl.	3	V. sl. wh. ppt.	Sl. cloud	Nil	Red br. ppt.
	Veronal <i>See Barbi- tone</i>								
276	Yohimbine Hydrochlor.	M. to br. liq. c. nause- ous od., ch., vaps.	About 300	100	100	Wh. ppt.	Yell. ppt.	Yell. ppt.	Red br. ppt.
277	Zinc Phenol- sulph.	Ch. c. od. of phenol	—	2	2½	Nil	Nil	Nil	Nil

BROM. AQ.	SPECIAL TESTS.
Yell. ppt., re-diss. c. opalescence	Usually has a faint garlic odour. Heated with lead hydroxide, hydrogen sulphide is removed.
Br. ppt.	Usually has slight garlic odour. NaNO_2 and HCl give brown ppt. Yellow ppt. with lead acetate, insoluble in dilute HNO_3 but blackened by conc. HNO_3 .
Turbid but no ppt.	Characteristic odour. Dissolved in 1 ml. glacial acetic acid and treated c. 0.3 ml. H_2SO_4 and 1 ml. HNO_3 , a bl.-gr. col. is produced.
Nil	Iodine separates on heating with H_2SO_4 .
Nil	Characteristic odour.
Nil	
Nil	Gives addition compounds with polynuclear hydrocarbons, e.g., naphthalene picrate (m.p. 150°) is pptd. on cooling 0.1 g. naphthalene and 0.2 g. trinitrophenol in 4 ml. dehydrated alcohol.
Yell. ppt.	Boiled with HCl , it is converted into benzoic acid and pseudotropine.
Nil	Heated above m.p., NH_3 is evolved and biuret formed which gives a reddish-vi. col. when dissolved in water, made alk. c. NaOH and treated c. 1 drop CuSO_4 sol. Urea nitrate pptd. from strong sols. by addition of HNO_3 . Decomps. c. hypobromite (<i>see also</i> Urine Anal. Chapter).
Nil	Heated with KOH it yields NH_3 , K_2CO_3 and alcohol.
Yell. ppt.	Mixed with powdered sucrose and H_2SO_4 it gives gr. col. turning blue. Heated with HCl on water-bath a blood-red solution is obtained. M.p. is indefinite.
Nil	The solid and sols. of the base turn or. on exposure. Becomes deep gr. and then yell. c. conc. HNO_3 , changing to cherry-red c. alc. KOH . Moistened c. H_2SO_4 and a crystal of $\text{K}_2\text{Cr}_2\text{O}_7$ passed through the liquid, a vi. col. is produced changing through blue to green. Mandelin's Reagent gives a vi. col. not becoming red on dil. c. wtr. (distinction from strychnine).
Decolourised	Yellowish-green ppt. c. $\text{K}_4\text{FeC}_6\text{N}_6$ insoluble in HCl .

TABLE OF THE COMMON ENZYMES AND FERMENTS

ENZYME OR FERMENT	CHIEF SOURCE	SUBSTRATE AND PRODUCT(S)
Amylase and Diastase ..	Human saliva, malt and pancreas.	Hydrolyses starch, forming dextrin and maltose.
Catalase (<i>see also Peroxidase</i>)	Blood, most animal and plant juices.	Decomposes hydrogen peroxide and other peroxides.
Cellulase ..	Grass-eating animals.	Converts cellulose into sugars as in the case of gramivorous feeders.
Emulsin ..	Almonds.	Hydrolyses glycosides, e.g. amygdalin.
Erepsin	Mucous membrane of small intestine.	Forms simple amino-acids from proteoses and peptones.
Fibrin Ferment (<i>see Thrombin</i>)		
Inulase	<i>Inula helenium</i> and squill.	Decomposes inulin, forming fructose.
Invertase or Sucrase ..	Intestinal juice and yeast.	Can convert many times its own weight of cane sugar into glucose and fructose.
Lactase	Animal body.	Converts lactose into glucose and galactose.
Lactic Acid Ferment (organised)	Lactic acid bacteria <i>q.v.</i>	Converts lactose into lactic acid.
Lipase	Pancreatic juice and seeds of plants.	Converts fat into fatty acids and glycerol.
Myrosin	Mustard seeds.	Hydrolyses the mustard glycoside in the presence of water.
Oxidases (<i>see Catalase and Peroxidase</i>)		
Papain	The juice of <i>Carica Papaya</i> .	Digests proteins in acid or alkaline solution.
Pepsin	Stomach, e.g., pigs.	Converts proteins into metaprotein, proteoses and peptone, in acid solution only.
Peroxidase ..	Blood, milk and many plant tissues, e.g., potato and fungi.	Oxidiser. Sets free oxygen from H_2O_2 . When an organic peroxide is in the plant tissue the system is called oxidase.
Perhydridase ..	Ditto.	Reducing agent.
Ptyalin	Saliva of the mouth.	Converts cooked starch into dextrin and maltose.
Rennin or Chymosin ..	Stomach of sucking animals, e.g., calf.	Coagulates the casein in milk effecting clotting.
Steapsin, or Lipolytic Ferment	<i>See Lipase.</i>	
Thrombin ..	Blood, after it is shed, in the presence of Ca salts.	Coagulates fibrinogen into fibrin, forming the clot.
Trypsin	Pancreas.	Converts proteins into amino acids and a polypeptide dilute alkali.
Urease	The soya bean and in urine, especially in catarrh of bladder.	Converts urea into ammonium carbonate.
Zymase	Yeast.	Converts sugars into alcohol and CO_2 .

SUBSTANCES	MELTING-POINTS		CONSISTENCE AT 11°
	°C	°F	
Oleum Theobromatis	30-35	86-95	Yellowish white, hard, brittle, and melts with ease.
Sevum Præparatum } equal parts	39	102·2	Rather hard and brittle, but melts with ease.
Oleum Theobromatis } equal parts	33-34	91·4-93·2	{ Stiff paste. Easily softened with the fingers. Suitable for thick
Paraffinum Molle	38-46	100·4-114·8	creams.
Oleum Theobromatis } equal parts	35	95	White and soft.
Paraffinum Molle	34-41	93·2-105·8	Soft, white, unctuous.
Unguentum Cetacei, B.P.C.	50-60	122-140	Hard, tough, and tenacious, tallowy.
Adeps	34-40	93·2-104	Yellowish, stiff, tenacious, unctuous.
Japan Wax	39-40	102·2-104	{ Hard. Melts easily between the fingers. Not so brittle as Oleum
Adeps Lanæ	47	116·6	Theobromatis.
Oleum Theobromatis } equal parts . .	42-50	107·6-122	Soft and unctuous.
Cetaceum	52	125·6	Crystalline, scaly and slippery.
Sevum Præparatum	51-52	123·8-125·6	Very hard white mass.
Cetaceum	48-51	118·4-123·8	Hard, glossy mass. Easily melts between the fingers.
Ceresin } equal parts	60-70	140-158	Hard, white and brittle.
Stearin	54-65	129·2-149	Hard, like good paraffin.
Paraffinum Durum	50-60	122-140	White, hard, crumbling substance.
Unguentum Resinæ, B.P.C.	54	129·2	Crystalline, hard and slightly greasy.
Adeps, 3; Cera Alba, 1	59	138·2	Stiff white pomade.
Adeps, Cera Alba, equal parts	58	136·4	Very hard, white mass.
Cetaceum, Cera Alba, equal parts	58-59	136·4-138·2	Hard as last, but not so white in appearance.
Cera Alba	62-64	143·6-147·2	White, hard, tenacious.
Carnauba Wax	83-86	181·4-186·8	Hard, yellowish or greenish.
Carnauba Wax 1, Oleum Amygdalæ 4	77-78	170·6-172·4	Stiff mass, melting easily.
Carnauba Wax 1, Oleum Amygdalæ 3	78-79	172·4-174·2	Stiff ointment of brownish colour.
Cera Alba, Oleum Amygdalæ, equal parts	60-61	140-141·8	Hard and wax-like.
Cera Alba 1, Oleum Amygdalæ 5	54	129·2	Stiff ointment.
Cera Alba 1, Oleum Amygdalæ 9	52-53	125·6-127·4	Stiff ointment.
Cera Alba 1, Oleum Amygdalæ 19	48-49	118·4-120·2	} Very soft creams.
Cera Alba 1, Oleum Amygdalæ 39	43	109·4	

THE ANALYTIC QUARTZ LAMP

Filtered ultra-violet light has been used by many workers in various analytical operations.

For certain purposes it has now been definitely adopted as an efficient means for the qualitative detection of many substances and as an aid to the examination of drugs and other substances especially with reference to the presence of adulterants. This subject is dealt with fully in *Fluorescence Analysis in Ultra-Violet Light*, by Radley and Grant (Chapman and Hall, 1933) and the following notes are taken partly from a paper on "The Use of the Analytic Quartz Lamp for Testing Drugs," by Danckwortt and Pfau (*Analyst*, Dec., 1927).

The *Hanovia Analytic Quartz Lamp* contains a quartz burner in which a mercury arc is produced in an evacuated tube of fused quartz which is entirely transparent to ultra-violet rays of wave-lengths between about 4400 and 2800 (Angström units).

The burner is enclosed in an upper light-proof casing, and the rays pass through a dark filter of special glass into the observation chamber, which is closed at the sides by curtains.

The rays have proved useful in the identification and testing of paper, dyes, oils and varnishes, in discriminating between natural and artificial tannins, in toxicological work, and in chemical analytical work generally.

The following alkaloidal substances show a more or less pronounced intensity which disappears when they are quickly removed from the influence of the rays.

Aconitine	distinct light blue.
Atropine sulphate	faint bluish.
Apomorphine	deep blue.
Berberine	distinct yellow.
Berberine hydrochloride	distinct yellow-green.
Quinine hydrochloride	pronounced light blue.
Quinine sulphate	pronounced light blue.
Cinchonine	light bluish.
Cinchonine sulphate	distinct clear white.
Codeine	light clear yellow.
Colchicine	distinct yellow-green.
Emetine	distinct yellow-red.
Hydrastine	distinct light green.
Morphine	pronounced light blue.
Narceine	pronounced yellow-green.
Narcotine	light greenish.
Papaverine	pale light yellowish.
Pilocarpine	white.
Piperine	faint bluish.
Solanine	pronounced light yellow.
Thebaine	reddish yellow.
Veratrine sulphate	marked light blue.
Yohimbine hydrochloride	deep yellow-green.

Alkaloid solutions, except in a few cases such as quinine, are not suitable for examination when contained in ordinary glass test-tubes. Solutions are allowed to permeate filter paper and coloured zones are observed when dried strips are placed under the lamp.

Danckwortt and Pfau give their observations on several solutions which were examined in this way. **Extracts and Tinctures** containing alkaloidal constituents may be examined similarly. Three extracts are taken of each drug, one neutral, one acid and one ammoniacal. The following capillary appearances have been observed:—

	IN NEUTRAL AND ACID SOLUTIONS	IN ALKALINE SOLUTIONS
inchona ..	Upper zone deep blue, lower strip red-violet.	No blue zone, no red-violet colouring.
elladonna	Upper zone broad yellow-green, underneath light bluish.	Dirty green, below red-brown, underneath no bluish shade.
igitalis ..	Above narrow blue-green zone, then green-brown.	No upper zone, deep dirty brown.
lyoscyamus	Upper zone light blue-green, dirty green, then bright.	Blue-green, underneath dirty green-brown.
tramonium	Faint narrow pale yellow zone.	Similar to the acid solution.
pium ..	Upper zone distinct light blue, underneath two yellowish zones.	Light blue, underneath several zones.
ecacuanha	Dark blue, underneath light blue.	No blue zones, faint light yellowish.
hydrastis ..	Upper zone dark blue, the other strip deep yellow.	Faint bluish wider zone, underneath deep yellow
reca ..	Upper zone distinct blue, underneath coffee-brown.	Fainter blue, underneath green-brown.
olchicum ..	Broad light yellow zone, underneath colourless.	Yellow zone fainter.
trophanthus	Narrow bluish zone, underneath darker zone, then lighter.	Wider lighter zone, yellow-brown, then light.
ux Vomica	Faint bluish, underneath at first dark green, then blue.	Light bluish, underneath no green zone.
eratrum ..	Dirty yellow-brown, underneath light greenish, then violet-blue.	Above faint light-bluish wider brown zone, then light green, later bluish.

Powdered Drugs. Some broken or powdered vegetable drugs give a fluorescence which is of value for their detection in mixtures, and when present as adulterants in other drugs. The freshly broken surface of **hydrastis** gives a characteristic bright yellow fluorescence, the scraped or broken surface of **gelsemium** gives a marked blue colour, **rhubarb** gives a reddish-brown fluorescence, and the method has been used for the detection of the presence of **montic rhubarb**, which gives a bright violet or lilac colour when viewed in ultra-violet light.

Other References:—*Ultra-Violet Rays and Their Properties*, by W. D. Gillivray; *Lumineszenz-Analyse im filtrierten ultravioletten Licht*, by P. W. Ackworth; *The Chemical Action of Ultra-Violet Rays*, by C. Ellis and Wells.

MICRO-CHEMICAL ANALYSIS

The chemical principles employed in methods of quantitative micro-chemical analysis are the same as those with which analysts are familiar in ordinary processes of analysis, but the operations are reduced in scale to about one-hundredth part of the normal, and saving of material, reagents, time and space are the chief factors responsible for the general adoption of many of the methods.

The names of Emich, Kuhlmann and Pregl are those to which chemistry is indebted for much of the technique of present methods. For a general account of the subject readers should refer to Pregl's *Quantitative Organic Microanalysis*. A useful and interesting summary of the methods suitable for general analytical practice is given by Professor H. V. A. Briscoe and Mrs. Janet V. Matthews in two lectures given in March, 1934, and published by the Institute of Chemistry.

Other References:—*Lehrbuch der Mikrochemie*, 2nd Edition, by Friedrich Emich; *Die Praxis der Quantitativen organischen Mikro-analyse*, by Friedrich Emich; *Handbook of Chemical Microscopy*, by Chamot and Mason; *Recent Advances in Analytical Chemistry*, Vol. II (Micro-chemistry), edited by Dr. Ainsworth Mitchell.

DROP MEASURE TABLE

By the International Agreement, 1930, a drop is measured by means of a tube which delivers in 20 drops 1 gramme of distilled water at 15°.

The following table gives the number of drops per millilitre of some substances included in the *B.P.* '32 and *B.P.C.* '34:—

Acidum Aceticum	42
Acidum Aceticum Glaciale	63
Acidum Hydrobromicum Dilutum	22
Acidum Hydrochloricum Concentratum	28
Acidum Hydrochloricum Dilutum	21
Acidum Hydrocyanicum Dilutum	22
Acidum Hypophosphorosum Dilutum	23
Acidum Lacticum	46
Acidum Oleicum	37
Acidum Phosphoricum Concentratum	34
Acidum Phosphoricum Dilutum	21
Acidum Sulphuricum Concentratum	53
Aether	65
Alcohol (90%)	53
Amylis Nitris	60
Aqua Cinnamomi Concentratum	50
Aqua Menthæ Piperitæ	55
Bromoformum	108
Chloroformum	82
Creosotum	43
Eucalyptol	51
Extractum Belladonnæ Liquidum	52
Extractum Colchici Liquidum	53
Extractum Ipecacuanhæ Liquidum	55
Extractum Nucis Vomicae Liquidum	55
Extractum Senegæ Liquidum	49
Liquor Adrenalinæ Hydrochloridi	28
Liquor Ammoniaæ Dilutum	22
Liquor Azorubri	23
Liquor Tartrazinæ Compositum	23
Oleum Anisi	41
Oleum Bergamottæ	51
Oleum Carui	47
Oleum Caryophylli	47
Oleum Cinnamomi	44
Oleum Crotonis	36
Oleum Eucalypti	51
Oleum Limonis	51
Oleum Menthæ Piperitæ	47
Oleum Myristicæ	53
Oleum Rosmarini	51
Oleum Santali	41
Oleum Sinapis Volatile	44
Oleum Terebinthinæ	48
Phenol Liquefactum	40
Spiritus Camphoræ	56
Spiritus Menthæ Piperitæ	56

STAINS, TO REMOVE

Stains	On cloth. Removed with:—	On the skin. Removed with:—
id, Picric	Sodium carbonate solution, hot	Sodium benzoate solution.
id, Pyrogalllic	First moisten with ferrous sulphate, and then wash in oxalic acid solution	On fingers, use pot. carb. 1 oz., chlorinated lime $\frac{1}{2}$ oz., water 4 oz., or add 1 or 2 dr. of sulphuric acid to $\frac{1}{2}$ pint of 25% sodium sulphite sol. and use $\frac{1}{2}$ oz. of this with 4 oz. of water. Ammonium persulphate solution is also good.
riflavine	Dilute HCl and bleach after	Sulphurous acid, or dil. H_2SO_4 and spirit.
omine	Sodium hydroxide solution	Dilute ammonia solution, or carron oil.
rbol Fuchsine	Sulphuric acid and water. Repeat several times if necessary	Sulphuric acid and water
chineal	Hot water	Soap and water.
ocus (Saffron)	Wash with HCl and boil with washing soda	Washing soda in water.
sin	Strong hydrochloric acid	Strong hydrochloric acid.
eric Chloride	Oxalic acid solution	Oxalic acid solution.
tian Violet	Dil. H_2SO_4 and hypochlorite as bleach after	Spirit.
ematoxylon (Logwood)	Render acid and then alkaline and bleach	Make alkaline and wash with hypochlorite.
anna	HCl and hot water	Hypochlorite
k, black	Oxalic acid, and finally bleach with hypochlorite	Soap and water.
k, red (if made with eosin)	Hydrochloric acid, and wash well	Strong hydrochloric acid.
l best red ink is made with eosin)		
t, typewriting (purple)	Dilute hydrochloric acid	Dilute hydrochloric acid
ine, Tincture of	15% to 20% warm sodium thiosulphate solution	
ethylene Blue	Wash with dil. H_2SO_4 and use hypochlorite after. Spirit also helps	Spirit removes easily.
assium Chromate	Washes out with water	Soap and water.
. Permang.	Sulphurous acid	Ac. tart., HCl, SO_2 , or thiosulphate.
er Nitrate	Wash with solution of iodine 2, pot. iod. 10, liq. ammon. 1, water 100, allow to soak in, then rinse with ammonia.	As for cloth.
acco Stains		Chlorinated soda sol. or pot. permang., followed by SO_2 .
nut Juice	Soap and hot water	Soap and water.

FREEZING MIXTURES

For cooling and setting suppositories, bougies, etc.

The following is a list of some freezing mixtures best prepared from commercial Crystalline Salts and in a thick wooden vessel:—

	Temp. reach °C.	°F.
Ammonium Nitrate 1, Water 1	—17	+1
Sodium Nitrate 3, Dilute Nitric Acid 2	—19·5	—4
Ice 2, Sodium Chloride 1	—20·5	—6
Ammonium Nitrate 1, Sodium Carbonate 1, Water 1 ..	—22	—8
Ice 24, Sodium Chloride 5, Ammonium Nitrate 5 ..	—28	—18
Ice 3, Sulphuric Acid 2	—30·5	—23
Ice 8, Hydrochloric Acid 5	—33	—27
Ice 3, Dilute Nitric Acid 2	—43	—41
Ice 8, Dilute Sulphuric Acid 10	—68	—90

SULPHURIC ACID, Sp. Gr. and Percentage Table, w/w

Sp. Gr.	%	Sp. Gr.	%	Sp. Gr.	%	Sp. Gr.	%	Sp. Gr.	%
1·020	3·03	1·165	22·83	1·330	42·66	1·530	62·53	1·760	82·4
1·035	5·23	1·185	25·4	1·355	45·35	1·560	65·08	1·785	85·1
1·055	8·07	1·200	27·32	1·380	48·00	1·590	67·58	1·805	87·6
1·070	10·19	1·220	29·84	1·400	50·11	1·620	70·32	1·820	90·0
1·085	12·3	1·240	32·28	1·425	52·63	1·645	72·4	1·832	92·5
1·105	15·03	1·265	35·14	1·450	55·03	1·675	74·97	1·839	95·0
1·120	17·01	1·285	37·45	1·480	57·83	1·705	77·60	1·842	97·7
1·145	20·26	1·305	39·77	1·505	60·18	1·735	80·24	1·8385	99·9

HYDROCHLORIC ACID, Sp. Gr. and Percentage Table, w/w

1·010	2·14	1·060	12·19	1·105	20·97	1·145	28·61	1·185	36·8
1·025	5·15	1·070	14·17	1·115	22·86	1·155	30·55	1·190	37·9
1·040	8·16	1·080	16·15	1·125	24·78	1·165	32·49	1·195	38·7
1·050	10·17	1·090	18·11	1·135	26·70	1·175	34·42	1·200	39·7

NITRIC ACID, Sp. Gr. and Percentage Table, w/w

1·020	3·70	1·150	24·84	1·280	44·41	1·390	63·23	1·465	81·4
1·040	7·26	1·170	27·88	1·305	48·26	1·405	66·40	1·475	84·4
1·060	10·68	1·185	30·13	1·325	51·53	1·420	69·80	1·485	87·7
1·085	13·95	1·210	33·82	1·345	54·93	1·430	72·17	1·495	91·0
1·100	17·11	1·235	37·53	1·360	57·57	1·445	75·98	1·505	96·3
1·125	21·00	1·260	41·34	1·375	60·30	1·455	78·60	1·520	99·0

POTASSIUM HYDROXIDE, Sp. Gr. and Percentage Table, w/w

1·014	1·7	1·108	12·9	1·220	24·2	1·357	35·9	1·530	49·7
1·029	3·5	1·125	14·8	1·241	26·1	1·383	37·8	1·563	51·9
1·045	5·6	1·142	16·5	1·263	28·0	1·410	39·9	1·580	53·9
1·060	7·4	1·162	18·6	1·285	29·8	1·438	42·1	1·597	54·9
1·075	9·2	1·180	20·5	1·308	31·8	1·468	44·6	1·615	55·9
1·091	10·9	1·200	22·4	1·332	33·7	1·498	47·1	1·634	57·9

SODIUM HYDROXIDE, Sp. Gr. and Percentage Table, w/w

1·014	1·20	1·125	10·97	1·252	22·64	1·345	31·22	1·438	39·7
1·029	2·71	1·142	12·64	1·274	24·81	1·357	32·47	1·453	41·7
1·045	4·00	1·162	14·37	1·285	25·80	1·370	33·69	1·468	42·7
1·060	5·29	1·180	15·91	1·297	26·83	1·383	34·96	1·483	44·7
1·075	6·55	1·190	16·77	1·308	27·80	1·397	36·25	1·498	46·7
1·091	8·00	1·210	18·58	1·320	28·83	1·410	37·47	1·514	47·7
1·108	9·42	1·231	20·59	1·332	29·93	1·424	38·80	1·530	49·7

Accumulator Acid Table.—*Pharm. J.*, i/1926, 357.

CHEMICAL TESTS & MICROSCOPIC METHODS FOR THE EXAMINATION OF URINE, BLOOD, FÆCES, STOMACH CONTENTS, &c.

URINE

The **quantity** of urine is increased in chronic interstitial nephritis, diabetes insipidus and diabetes mellitus. It is decreased in severe diarrhœa, fevers, uræmia and conditions which interfere with the circulation through the kidneys.

The yellow **colour** is due to pigments, e.g., urochrome. Blood pigment gives a red or brown, smoky colour. Urine which changes to a red colour on adding alkali is sometimes passed by patients taking phenolphthalein. Dark black urine suggests alkaptonuria, melanotic tumours or phenol poisoning. Bile pigments give an orange or brown colour, the colour being imparted to the froth on shaking.

The normal **reaction** is slightly acid (pH 6·0), due partly to acid phosphates and partly to free organic acids. Urine may become slightly alkaline after a full meal. On standing, it becomes alkaline owing to decomposition of urea and formation of ammonia. A similar marked alkalinity of freshly voided urine may be due to ammoniacal decomposition and may occur in severe cases of chronic cystitis.

The **specific gravity** of urine at 60°F. is usually between 1·015 and 1·025. It is low in chronic interstitial nephritis, diabetes insipidus and many functional nervous disorders. It is high in fevers and diabetes mellitus.

The **total solids** of the urine of a healthy adult amount to about 60 grammes or 950 grains per diem. A quick clinical method of determining the total solids is to multiply the last two figures of the specific gravity by the number of ounces voided and to add one-tenth of the product. This gives the amount in grains, e.g., $45 \times 20 = 900 + 90 = 990$ grains.

For **quantitative examinations**, a sample of the 24 hours excretion should be examined. For most **qualitative** examinations the first morning specimen is the best. In the case of female patients, where a microscopical examination is required, a catheter specimen should be obtained if possible.

Microscopic Examination.

The chief objects to be sought for are blood, pus, epithelium, casts, chemical deposits (crystalline or amorphous) and parasites. The centrifuged deposit or sediment should be used; a drop on a slide is covered with a cover slip and studied with a 2/3 and 1/6 inch objective. For accurate estimation of red blood cells or pus, the cells in the fresh uncentrifuged urine should be counted in a Fuchs Rosenthal cerebrospinal fluid counting-chamber. *Blood dealt with on p. 337.*

Epithelium.

Epithelial cells are present in normal urine and have no pathological significance. They are larger than pus cells, rarely round, usually non-granular and have a small central nucleus. It is impossible to determine the region of the urinary tract from which epithelial cells have been derived, but a rough classification may be made. Angular squamous epithelium comes from the vagina. Cells from the ureter or pelvis of the kidney are small and round, resembling polymorphonuclear leucocytes except that their nuclei are definitely round. Such cells are commonly seen in specimens collected by ureteric catheterisation and must be distinguished from pus corpuscles. Fragments of tumours of the urinary tract should be teased out and stained, or, better, cut into microscopic sections. The recognition of isolated cells from a neoplasm is impossible.

Chemical Deposits.

The detection of a crystalline or amorphous deposit in the urine is no evidence that this substance is being excreted in excess, and in a case of calculus the chemical composition of the urinary sediment does not necessarily indicate the nature of the stone.

In acid urine, the only urinary deposits likely to be found are urates, uric acid, calcium oxalate, stellar phosphates and cystine. Urates are amorphous, brown or pink, and disappear on warming. Uric acid appears in many different forms as yellow or brown crystals which are soluble in sodium hydroxide (or lithium carbonate) and reprecipitated by hydrochloric acid. Calcium oxalate occurs as clear, colourless, octahedral crystals with an envelope appearance, or as dumb-bells. The crystals are insoluble in acetic acid but readily soluble in hydrochloric acid. Stellar phosphates are composed of calcium hydrogen phosphate and are readily soluble in acids. They appear when the urine is near neutral. They form long, narrow, flat prisms which are frequently collected in bunches or rosettes, or which may be fine and feathery. Cystine occurs only in patients with the rare congenital abnormality of cystinuria. The crystals occur as irregular hexagons with clear-cut straight sides; they are insoluble in acetic acid and ether, but soluble in hydrochloric acid and in ammonium and other alkalis. They occur only in acid urine.

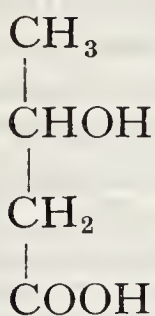
In alkaline urine, the commonest deposits are ammonium urate, amorphous phosphates, triple phosphates, calcium carbonate and calcium oxalate. Stellar phosphates sometimes occur. Ammonium urate forms a brownish deposit, soluble on warming. Amorphous phosphates form a white amorphous deposit, soluble in acetic acid. Triple phosphates form clear colourless crystals of various shapes and sizes, the typical ones being shaped like a knife-rest; they are soluble in acetic acid. Calcium carbonate forms a white deposit which may be amorphous or consist of dumb-bell shaped crystals. It dissolves in acid with effervescence.

In cases of acute liver atrophy, leucine and tyrosine may be found in the urine. Leucine crystals appear as yellow spheroids, with radial and concentric striations, and are soluble in acids and alkalis. Tyrosine forms brush-like tufts of fine needles which are soluble in ammonia and hydrochloric acid, and insoluble in acetic acid.

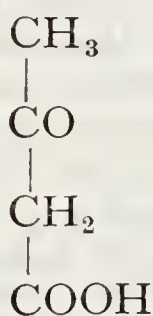
The following constituents of urine are dealt with in approximately alphabetical order.

ACETONE AND ALLIED BODIES

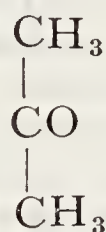
The bodies which often form abnormal urinary constituents comprise acetone, acetoacetic acid and β -hydroxybutyric acid. Their presence is usually due to the incomplete metabolism of fat, for example when the tissues are deprived of carbohydrate. The chemical relationship between them is shown thus:—



β -Hydroxybutyric acid



Acetoacetic acid



Acetone

Quite probably β -hydroxybutyric acid and acetoacetic acid are normally formed in the body during the splitting up of fat, but they are then fully oxidised.

It may be observed that the clinical significance of either acetoacetic acid or acetone (β -hydroxybutyric acid is not usually tested for) is the same.

Tests for Acetone Bodies.

Gerhardt's test consists in adding 10% ferric chloride solution drop by drop to the urine. At first a precipitate of ferric phosphate appears which redissolves in excess of the reagent. If acetoacetic acid is present in a concentration of 0.07% or over, the solution turns a Bordeaux-red colour. The colour should be compared with that obtained on adding ferric chloride to normal urine. A positive reaction indicates a severe degree of ketosis but a negative reaction does not signify that the patient is free from the dangers of ketosis. This is partly owing to the relative insensibility of the reaction and partly owing to the fact that acetoacetic acid is converted on standing into acetone, which does not respond to Gerhardt's test. Various drugs cause similar coloration with ferric chloride, but such fallacies are easily overcome by boiling another sample of the urine prior to testing. If the colour be due to acetoacetic acid, a negative reaction will be given by the boiled urine because the acid is volatile. The colour due to drug derivatives on the other hand is not affected by previous boiling of the urine.

Rothera's test for acetone and acetoacetic acid is a much more delicate test for ketosis. About 20 ml. of urine should be saturated with ammonium sulphate and a few drops of freshly prepared dilute solution of **sodium nitroprusside** $\text{Na}_4\text{Fe}_2(\text{CN})_{10}(\text{NO})_2\cdot 4\text{H}_2\text{O}$ (soluble 1 in $2\frac{1}{2}$) added. 2 or 3 drops of 10% ammonia is added and the tube shaken. If the reaction is positive, a delicate permanganate tinge develops and gradually deepens. A brown colour does not constitute a positive reaction.

Legal's test is similar. The nitroprusside is added to the specimen or to a distillate made slightly alkaline with potash. A red colour, changing rapidly to yellow, is positive. Acetic acid added gives a reddish-violet colour changing to blue.

The amount of acetoacetic acid can be judged by the depth of the colour and the rapidity with which it develops. A quick strong reaction corresponds to 0.25% and a slow weak reaction to 0.0005%. Intermediate reactions indicate proportional concentrations of acetoacetic acid (Kennaway).—There are no fallacies in Rothera's test. A moderately strong positive Rothera's test is not of such grave importance as a positive Gerhard's reaction.

The limiting concentration in Legal's test is, for acetoacetic acid, 6 mg. per litre, and for acetone 100 mg. per litre.—*J. chem. Soc. Abstr.*, 1925, 1490.

★**"Endolytic Tubes"** (cf., p. 308 and **glucose tests**) are made containing sodium nitroprusside and ammonium chloride to be used in conjunction with a little washing soda or potassium hydroxide, and also ferric chloride.

A large drop of urine is placed on a sheet of notepaper and saturated with crystal of soda. The saturated urine is allowed to run up a tube, the reagent having been shaken to the lower end. If acetone is present in quantity a petunium colour develops in about 30 seconds, and even with small amounts a rosy or amethyst flush is noticeable in a minute or two. If absent, the powder dissolves with a pale straw coloration.—*M. Fawkes, Brit. med. J.*, i/1925, 241.

Iodoform Test. Distil the sample, make the distillate alkaline with potash, and add a little iodine solution (not an alcoholic solution). The formation of iodoform, recognised by the yellow turbidity and the odour, indicates presence of acetone. *Microscopic examination* is more conclusive than the odour.

Determination of acetone in urine—formation of iodoform in the usual way, converting into silver iodide, and weighing.—*Yearb. Pharm.*, 1919, 56.

Scott-Wilson Test. Place one drop of Scott-Wilson reagent (see p. 32) on a microscopic slide and invert slide to form a hanging drop. Place the slide over the mouth of a flask containing the urine or blood and leave for 2 minutes. When acetone is present, the drop shows a fine white clouding or precipitate. A rough estimation of the amount of acetone present may be obtained as follows:

Faint trace	Opalescence	0.005%
Trace	Faint turbidity	0.01%
Moderate trace	Turbid	0.025%
Heavy trace	More marked	0.05%
Moderate amount	Very marked	0.075%
Large amount	Precipitate	0.1%

Compare by setting up a series of tubes containing acetone from 0.1% down to 0.005%.—*A. Wallhauser, J. Amer. med. Ass.*, ii/1928, 21.

Riegler's Test. Differentiates acetone and acetoacetic acid in urine. 10 ml. of the specimen is acidified with 5 drops

10% acetic acid and 5 drops of Lugol's iodine solution is added. Shake out with 2 to 3 ml. of chloroform. No colour appears if acetoacetic acid is present. The iodine is absorbed by the acetoacetic acid, forming a colourless compound.

Hurtley's Test for Acetoacetic Acid. To 10 ml. of urine add 2.5 ml. of concentrated hydrochloric acid and 1 ml. of 1% sodium nitrite. Shake and allow to stand two minutes. Add 15 ml. of strong ammonia followed by 5 ml. of 10% ferrous sulphate or a solution of ferrous chloride of equivalent strength (2 g. Fe in 100 ml.). Shake and pour into a 50 ml. Nessler glass. Do not alter. Violet colour forms slowly.

Acetone does not respond to the test, which is exceedingly delicate. It is assumed that isonitroacetone is first formed which then colours with the ferrous sulphate. The test can be rendered quantitative colorimetrically. As much as 0.4% has been found.

Colorimetric method for the determination of acetone bodies in blood, based on a reaction with salicylaldehyde.—*Yearb. Pharm.* 1927, 93.

The acetone content of the blood is 43.5% higher in pregnant than in non-pregnant women. During the second stage of pregnancy it reaches 12 mg. per 100 ml. of blood, returning to normal shortly after delivery.—per *J. Amer. med. Ass.*, ii/1925, 861.

Iodine Absorption Test, Bela and Ondrovich.—5 drops of acetic acid 10% is added to 5 ml. of urine, then 1 drop of 1 in 500 methylene blue or s. to give blue tint. Titrate with N/10 iodine solution until a red tint appears— $2\text{I} = \text{CH}_3\text{CO} \cdot \text{CH}_2\text{COOH}$.

Iodic Acid Test.—Add to 1 or 2 ml. of normal urine 2 ml. of 10% iodic acid solution and 3 ml. of chloroform. Uric acid, etc., reduces the iodic acid—the chloroform becoming coloured with the iodine. Add 10 ml. of the specimen to be tested, and shake thoroughly. If acetoacetic acid is present the colour disappears, if absent it is intensified.

β -Hydroxybutyric acid may be extracted from the specimen with ether and gives a reddish-violet colour with ferric chloride—the acetoacetic acid gives approximate index of the content of this acid. It occurs only if acetoacetic acid also present. The specimen may be fermented to remove sugar, precipitated with lead acetate and ammonia; if the filtrate is lævorotatory, β -hydroxybutyric acid is probably present.

Sellard's Test for Acidosis in Diabetes. (*Suggested by MacLean*). This depends on the ability of a normal individual to secrete an alkaline urine after taking 5 to 10 g. of sodium bicarbonate. In acidosis, the excess of acids combines with the alkali, forming a neutral salt, and much larger doses have therefore to be given. The reaction of the urine is tested with litmus paper 1 hour after successive 5 g. doses of sodium bicarbonate, the urine being first boiled and cooled. The amount of alkali required to render the urine alkaline gives an indication of the degree of acidosis, 30 to 60 g. being necessary in moderate cases.

ALBUMIN

Albuminuria may occur in healthy individuals, as functional or postural albuminuria. The albuminuria may disappear when the patient is at rest, to reappear on taking exercise or even on assuming the erect posture. In pathological conditions, albuminuria is nearly always accompanied by tube casts and under these circumstances it points to organic disease of the kidney, or to severe irritation or circulatory changes in the kidney.

(*Renal function tests are dealt with on p. 327 et seq.*).

The amount of albumin detected at any time does not measure the degree of the albuminuria. A large output naturally implies failure of nutrition, but a small quantity may be of equal danger. Note sp. gr. and colour.

The mere presence of albumin in the urine of adolescents need not be regarded so gravely as was once the case, provided there are no other signs of renal or constitutional disability. One in every twenty male adolescents exhibits the condition, which may persist throughout life without detriment to physical efficiency. The after-rest specimen is usually free from albumin. The condition is not associated with any particular type of youth or man.—H. H. Bashford *Lancet*, ii/1926, 1305-7.

Pure albumin free from globulin can be isolated from the urine by repeated precipitation with sodium sulphate. In cases of albuminuria of pregnancy (and proteinuria not associated with pregnancy) the albumin had a specific rotation averaging -55.81° , whereas in eclampsia there were two groups averaging -56.37° and -38.5° . Accordingly, it is suggested that in certain types of eclampsia the urinary albumin may be mainly *lactalbumin*, and that eclampsia may be an anaphylactic reaction due to the circulation in the blood of this foreign protein, in the production of which the mammary gland may be an important factor.—A. Hynd, *Lancet*, ii/1925, 911, 925.

Tests for Albumin in Urine.

The simplest and most accurate test is to boil the top of a column of urine in a test-tube, and if a turbidity appears in the part boiled, add a drop of 5% to 10% acetic acid. Phosphates are dissolved but albumin remains. The delicacy of the test depends on the contrast between the upper and lower region and the urine must be filtered if it is not clear before the test is conducted.

The only substance likely to mislead is **Bence-Jones proteose**, a variety of protein excreted by patients suffering from multiple myelomata, and occasionally by cases of leukæmia and chronic nephritis. Bence-Jones proteose appears when the urine is heated to about 50° and disappears on boiling, to reappear when the urine cools.

Salicylsulphonic Acid Test. This has the advantage that it can be performed in the cold. An equal volume of urine is placed in two test-tubes and 2 or 3 drops of 25% solution of salicylsulphonic acid added to one of them.

In the presence of albumin the liquid in the tube to which salicylsulphonic acid was added will appear turbid compared with the control.

The urine of patients who have been given Uroselectan gives false positive reaction with salicylsulphonic acid but not with the boiling test.

It is an extremely precise, reliable, and quick test, giving a dense white precipitate.

In confirmation note the following:—

Albumin, globulin, myosin, etc., coagulate on heating.

Albumoses dissolve on heating, and reappear on cooling.

It is not affected by phosphates, bile, urates or alkaloids.

Pure peptone is not precipitated, only the intermediate product between albumin and peptone, in solutions saturated with ammonium sulphate.

Albuminuria. Incidence in 60,000 men examined. Salicylsulphonic acid used. It is undoubtedly one of the most reliable and delicate reagents—6 drops of saturated solution to about $\frac{1}{2}$ inch of urine in an ordinary test-tube. Total with gross albuminuria after allowing for pus, etc., about 5%.—H. Maclean, *Brit. med. J.*, i/1919, 94.

Nitric Acid Test (Heller's).

Nitric acid is placed in a test-tube and the filtered urine, or diluted filtered urine, carefully "layered" on to it. A white ring at the junction of the liquids indicates presence of albumin; confirm by heat and salicylsulphonic tests. Not so delicate as the **heat and acetic acid test**, but will show 1 in 12,000 at once. Urines containing bile pigments may produce a play of colours characteristic of Gmelin's test.

Picric Acid Solution (Esbach's Reagent).

Picric acid 10 g., citric acid 20 g., dissolved in about 900 ml. of boiling water; cool and add water to 1000 ml. This reagent is used for the approximate determination of albumin by an albuminometer which is about six inches long and 0.6 inch in diameter; the graduations on it are the results of experiment and indicate approximately 0.1% up to 0.7% of albumin.

By comparison with a standard dried albumin solution, 1 in 1000, and by heating both to 180°F. and centrifuging, the process can be terminated in a few minutes.

Mann warns against the voluminous precipitate which one occasionally gets with Esbach's reagent, giving a fictitious estimation. Many albuminous urines give a pale blue with the Biuret reaction without any tendency to violet; others will give a reddish-purple. Such urine indicates by the reddish colour some hydrolytic change and will give the incorrect reading referred to.

For exact determinations, albumin should be precipitated by some suitable reagent, itself nitrogen-free, e.g., carbolic acid or tannin, and the washed precipitate, dried and weighed, or better, the nitrogen contained in it should be estimated by a Kjeldahl analysis, the amount of nitrogen found being multiplied by the factor 6.3 to obtain the amount of proteins.

N.B.—Methylene blue precipitates picric acid solution in case of patients undergoing treatment with this compound.

The administration of alkaloids may cause urine to give a precipitate with picric acid, but this is redissolved on heating to the boiling point.

Ferrocyanic Acid (Hydroferrocyanic Acid) Test.

Potassium ferrocyanide and acetic or citric acid mixed in solution set free hydroferrocyanic acid. Does not precipitate peptones.

The following procedure may be used:—

Solution A.—Citric acid 10 g.; water 100 ml.

Solution B.—Potassium ferrocyanide 10 g.; water 100 ml.

Add 3 ml. of solution A to 4 ml. of the specimen. Mix and add 3 ml. of solution B. In the presence of 0.3% or more of albumin an immediate precipitate is formed. 0.1% is detected on standing for one hour. May also be applied as a ring test.

1 ml. of a 10% solution of acetic acid and potassium ferrocyanide gives a just perceptible clouding when added to urine containing 0.1% albumin diluted in 100 with water. If the clouding appears with a dilution of 1 in 200 the urine contains 0.2% and so on.—*Brit. med. J. Epit.*, ii/1927, 78.

Further Chemical Tests for Albumin Detection.

Trichloroacetic Acid. A saturated solution, or a crystal, is used in the same manner as in the salicylsulphonic acid test. May precipitate uric acid and nucleoproteins.

Tannin-hydrochloric Acid Test. Mix 5 ml. of the specimen with 5 ml. warm 1·5% alcoholic tannin solution and add 5 ml. of dilute hydrochloric acid (1 in 3). Turbidity or yellowish precipitate. Interfering substances, such as urates, phosphates and alkaloids, are kept in solution by the acid; resins and alkaloids are redissolved by the alcohol, and peptones by heating.

Roberts' Albumin Test. Nitric acid 1 part, solution of magnesium sulphate (10 in 13) 4 parts. Is found to be very satisfactory—advantage, high density. Slope the tube containing a little test solution and allow the urine to run down into it slowly with a dropper. Ammonium nitrate may be used instead of magnesium sulphate.

Metaphosphoric Acid, HPO_3 . A fresh solution of a little of this acid is added to the clear filtered urine. A cloud or precipitate indicates presence of albumin.

Millon's Reagent. Dissolve mercury 3 ml. in fuming nitric acid 27 ml. without heat, and dilute the resulting solution with an equal volume of distilled water. With albumin or urea this gives a yellow, then a red coloration on heating.

The directions given above are those of the *B.P.* '32. Many modifications of Millon's reagent have been proposed. The following, for example, is one-third of the strength of the *B.P.* '32 solution in mercury and is possibly the original formula. Dissolve mercury 1 by weight in nitric acid 2 by weight and then dilute with 2 volumes of water.

Asaprol (calcium β -naphtholsulphonate) precipitates albumin, peptone etc., from acid solution. On boiling, peptone and albumose redissolve, albumin remains.

*** Endolytic tubes (albumin).** Sealed capillary tubes partially filled with a solution of salicylsulphonic acid are convenient for clinical use. The ends are snapped off and the urine (if necessary, filtered) is drawn into the tube by capillarity. An opalescence to a thick precipitate occurs if positive. Distinguish albumose by pouring hot water over the tube—the precipitate dissolves as above detailed. *Acetone, diacetic acid and glucose Endolytic tubes* are also made.

ALBUMOSES

One may safely regard all proteins in urine which dissolve on heating (after precipitation by a reagent, e.g., salicylsulphonic acid) and reappear on cooling, as albumoses.

Biuret Reaction.—Albumin, if present, is removed by 10% trichloroacetic acid solution, and the filtrate tested with the *Biuret Test*:—

In a test-tube place 1 drop of copper sulphate solution (2%) add 5 ml. of urine, and then 5 ml. of sodium hydroxide solution (10%). *A rose pink indicates the presence of albumose.*

Nickel Reagent. 2 ml. of a solution of 5% nickel sulphate with strong ammonia is added to 4 to 5 ml. of urine made strongly alkaline with potassium hydroxide. Protein present gives a white or greenish-white ring, while an *orange yellow ring* is given in the presence of *albumoses and peptones*.—*J. chem. Soc. Abstr.*, ii/1921, 419.

Albumose, Bence-Jones, occurs in myelopathic albuminuria, a disease associated with morbid conditions of the bone marrow. This albumose is detected by (1) coagulating at 50° or lower, i.e., lower than serum albumin, which coagulates at 75° (on raising to the boiling-point, however, the coagulum dissolves more or less completely, reappearing on cooling). The coagulation point is considerably influenced by the reaction of the specimen. The resolution of the albumose at 100° may not

complete owing to presence of other proteins; (2) precipitation with concentrated hydrochloric acid; (3) precipitation with nitric acid in the cold—on raising to the boiling-point, however, the coagulum dissolves more or less completely, reappearing on cooling; (4) precipitation with potassium ferrocyanide and citric acid (often takes time to develop, differing in this respect from albumin). The hydrochloric acid test is exceedingly sensitive and does not depend on excess of salts. The result is obtainable after very free dilution of the specimen. Some specimens of urine containing a high concentration of albumin give false positive reactions with the hydrochloric acid test.

AMINO-ACIDS

Tyrosine (*p*-hydroxyphenylalanine), $\text{OH} \cdot \text{C}_6\text{H}_4 \cdot \text{CH}_2 \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$, is recognised by its characteristic crystalline appearance, being in shining needles, either in bundles or star form. When tyrosine appears in urine it is usually associated with bile pigment, and the crystals may acquire a yellow colour. The crystals are soluble in mineral acid, but insoluble in acetic acid, acetone, alcohol and ether.

Russula delica.—The juice of this fungus is used as a test for tyrosine, which changes it from red to black. The fungus has a stem 1 to 2 inches high, $\frac{1}{2}$ inch or more thick; an even, smooth, white cap, which is fleshy, 3 to 5 inches broad, and funnel-shaped when fully grown; a regular, even, smooth margin, involute, without striæ, and flesh which is firm, dry and white.

Further Tests for Tyrosine:—

2 ml. of sulphuric acid mixed with 3 to 5 drops of a solution of aldehyde in twice its volume of alcohol 90%, care being taken that the liquid remains colourless—a few drops added to the suspected liquid produces a gooseberry-red colour. This test is supposed to detect tyrosine in a dilution of up to 1 in 10,000.

Piria states that on adding a few drops of strong sulphuric acid to a little tyrosine in a dish it dissolves with slight reddening on saturating with barium carbonate (after diluting), and on adding to the filtrate neutral ferric chloride solution a violet colour is formed.—Schmidt.

Ammonium sulphomolybdate, *q.v.*, gives a blue to violet colour.

Leucine (*α*-aminoisocaproic acid), $(\text{CH}_3)_2\text{CH} \cdot \text{CH}_2 \cdot \text{CH}(\text{NH}_2)\text{COOH}$, occurs as an early result of protein cleavage. There are two isomeric forms of it—*lævo*- and *dextro*-leucine. It occurs in crystalline spheroidal clumps, and is an arterial depressor.

Histidine, $\text{C}_6\text{H}_9\text{N}_3\text{O}_2$, is one of a series of bases termed protamines which give the biuret reaction.

BILE AND ITS DERIVATIVES

The presence of either **urobilin**, **bile pigments** or **bile salts** in the urine indicates some derangement of hepatic functioning. Urobilin is found in small quantities in normal urine, but insufficient to be detected by the ordinary tests. It is formed from urobilinogen, a decomposition product of bilirubin formed by the action of the intestinal bacteria on the bile which passes into the intestine. Under normal conditions a portion of this is absorbed from the intestine and carried to the liver in the portal blood and is there reconverted into bilirubin. When the liver functions are

deranged this transformation into bilirubin may be interfered with and urobilinogen reaches the general circulation and is excreted by the kidneys. Thus, tests for urobilin may be positive in the pre-icteric stage of jaundice. Urobilin is increased as the result of excessive blood destruction and in damage to the liver parenchyma. It is nearly or completely absent in obstructive jaundice.

Bile pigments and bile salts usually occur together, although the bile pigment may occur alone. It is seldom necessary therefore, to test for bile salts. The significance of bile in the urine is similar to that of bile staining of the tissues, and is attributable to obstruction of the outflow of bile from the liver. Small amounts of bile may, however, be found in the urine when the disturbance is not severe enough to produce recognisable jaundice, or in other cases before the jaundice supervenes.

Bile pigments are simply demonstrated by **Gmelin's Test**. Urine is "layered" over the surface of strong fuming nitric acid in a test-tube. With normal urine a purple or yellow colour may appear, but in the presence of bile pigment a green colour develops at the junction of the fluids.

Tincture of Iodine. A few drops diluted with three times as much water "layered" on to the specimen, and the tube shaken gently, produce a green colour if bile pigment is present.

Chromic Acid. A 5% solution added gradually produces a green colour. The following is a modification:—

To 10 ml. of urine add 2 ml. of 0.5% solution of albumin and a few drops of 10% acetic acid; boil and filter. Wash the precipitate with water and to it, on the filter, add 1 drop of a mixture of 4 ml. of 6% potassium dichromate and 1 ml. of 20% sulphuric acid. If bile pigments are present the yellow precipitate turns green or bluish-green. This sensitive reaction is not given by other normal or abnormal urinary pigments.—*J. chem. Soc. Abstr.*, ii/1922, 671.

Sodium Nitrite with sulphuric acid (**Vitali's Reaction**) gives a green colour.

Ferric Chloride Test. **Obermayer Reagent** prepared by dissolving 0.3 g. of ferric chloride in 100 ml. of concentrated hydrochloric acid. 0.5 ml. of the reagent is added to 5 ml. of urine, and if bile pigment is present the colour at once appears as a deep green—bile may be tested in the same way. For serum 4 ml. of 95% alcohol is added to 2 ml. of serum and centrifuged, the supernatant liquor withdrawn and 0.5 ml. of reagent added—a green colour will appear in a few seconds.—*Prescriber*, 1924, 300.

The following modification suggested by Harrison has proved very useful for the detection of traces of bile pigment. To 10 ml. of urine add about 5 ml. of 10% barium chloride; mix and filter. To the precipitate on the filter paper add 1 or 2 drops of Fouchet's reagent. The presence of bile pigments is shown by a green colour.

Fouchet's Reagent: trichloroacetic acid 20 g., 10% ferric chloride 10 ml., water 100 ml.

Clinical tests for bilirubin in urine.—E. M. Godfried, *Biochem. J.*, 1934, 2057; Hunter, *Can. med. Ass. J.*, 1930, 23, 823.

The Van den Bergh Test (*vide infra*) is the best for qualitative and quantitative examinations of blood for bile pigments.

Bile Salts are shown by **Hay's Test**. Flowers of sulphur is sprinkled on the surface of cold urine in a beaker. The powder floats on the surface of normal urine. Bile salts lower the surface tension and permit the sulphur to sink.

Pettenkofer's Test.—Add a few drops of syrup, shake, and then add sulphuric acid—a reddish-violet colour (cf. acid cholalic and sodium tauroglycocholate in *Scheme for Recognition of Organic Substances*).

Peptone Test. Peptone, in powder 30, salicylic acid 4, acetic acid 30, distilled water 3500. Dissolve and filter. On adding one volume of urine containing bile salts to three volumes of this solution opalescence (or precipitate) appears; it dissolves completely on adding acetic or citric acid, and diminishes, but does not disappear, on boiling.

Urobilin

Spectroscopic Examination. Urine acidified with a little hydrochloric acid shows an absorption band at the junction of the green and blue.

Schlesinger's Test. Urine 10 ml., tincture of iodine 3 to 4 drops. Add to this 10 ml. of alcohol containing about 1 g. of zinc acetate in suspension, shake well and filter. The filtrate by transmitted light will appear yellow or pink. By reflected light it will show a marked green fluorescence. In the above tests any urobilinogen will be converted into urobilin by the hydrochloric acid and iodine respectively.

LIVER FUNCTION TESTS

Van den Bergh's Reaction (Ehrlich's Diazo Reaction applied to blood serum containing bilirubin) for obstructive or impaired liver function.

The reagent consists of: *Solution I.* Sulphanilic acid 1, hydrochloric acid B.P., 15, water to 1000. *Solution II.* Sodium nitrite 0.5, water 100. For use, 25 ml. of solution I is mixed with 0.75 ml. of solution II; this mixture must be freshly prepared for each test.

Direct Test (Qualitative). Add 1 ml. of the reagent to an equal volume of serum diluted with 2 ml. of distilled water. A bluish-violet colour beginning immediately and becoming maximal in 10 to 30 seconds is called an immediate direct action, indicating presence of uncombined bilirubin and the existence of mechanical obstructive jaundice. A reddish coloration beginning after 1 to 15 minutes and deepening to violet is called a delayed direct reaction. A reddish colour appearing at once and deepening to violet is called a biphasic direct reaction.

Indirect Test (Qualitative). To 0.5 ml. of serum add 1 ml. of 95% alcohol and centrifuge. To 1 ml. of the supernatant fluid add 1 ml. of reagent. If positive a violet colour appears at once.—*J. Amer. med. Ass.*, ii/1928, 1395.

Indirect Test (Quantitative). To 1 ml. of serum in a 15 ml. graduated tube add 0.5 ml. of reagent. After a minute or two add 2.5 ml. of 95% alcohol and 1 ml. of saturated ammonium sulphate solution. Mix well and centrifuge. Read the quantity of supernatant fluid, and the dilution of the bilirubin (approx. 1 in 3) contained in the serum is directly obtained (dilution of unknown). The alcohol solution (the unknown) is then compared with a standard solution and the amount of bilirubin computed as follows:

$$\frac{\text{Standard}}{\text{Unknown}} \times \text{Dilution of unknown} \times 5 = \text{mg. of bilirubin per litre of serum.}$$

The standard is made as follows: *Solution I.* Ammonium ferric alum 0.1508 g., conc. hydrochloric acid 50 ml., distilled water to 250 ml. (keeps indefinitely). *Solution II.* Of solution I, 10 ml., conc. hydrochloric acid 25 ml., distilled water to 250 ml. (keeps a month). The standard, which is freshly made, consists of solution II, 3 ml. of ammonium thiocyanate 10% or 3 ml. of potassium thiocyanate 20%, ether 12 ml.

Shake the standard thoroughly. The ether extracts the colour from the solution and forms a supernatant layer which may be used in colorimetric comparison. The standard matches in colour a dilution of 5 mg. of bilirubin per litre of serum. The normal amount of bilirubin is from 1 to 3 mg. per litre.

Standard for Van den Bergh's Test. The colour given by 0.7 ml. of N/10 potassium permanganate diluted to 50 ml. with water is equivalent to 1 in 10⁶ of bilirubin.—*Brit. chem. Abstr.*, 1928, 1048.

Extensive clinical trial has shown that its claim to distinguish obstructive jaundice from catarrhal, toxic and infective jaundice is untenable. In actual practice, the direct reaction is seldom met with. In its usual form it would be

more correctly described as a change from the original yellow, through red to a red-violet, or violet, beginning at once on the addition of the reagent, the process taking from several minutes up to half an hour—though this is essentially a description of the “biphasic reaction” as given by Van den Bergh. To avoid this difficulty the reaction is said to be (1) *direct* when the colour change begins on the addition of the reagent, whilst not more than a trace of the total pigment is extracted when another sample of the serum is shaken with an equal volume of chloroform (judged by colour of chloroform layer as compared with colour of serum) (2) *biphasic* when colour change begins on addition of reagent whilst an appreciable proportion of the pigment is extracted by the chloroform (3) *indirect* when no change of colour occurs with the reagent until after the addition of alcohol to the serum.—W. M. Roberts, *Brit. med. J.*, i/1933, 734.

The test is less satisfactory than at first hoped. Very variable results obtained in toxic cases. In genuine obstructive cases, immediate direct reaction was obtained, and in hæmolytic cases an indirect reaction. In doubtful cases the test failed.—*Brit. med. J.*, i/1924, 279; see also *ibid.*, 496, and *Lancet*, i/1927, 384.

The test for “latent” jaundice, during treatment with arsenobenzol, has been found of greater value than either the Lævulose Tolerance Test, the Lipase Test or the “Hæmoclastic Crisis” Test, and is a great advance towards some scientific control in the use of this dangerous drug. As soon as a condition of “latent” jaundice was detected arsenical treatment was at once stopped and glucose given freely. The small amount of serum necessary for the test is readily obtained when taking blood for Wassermann reactions.—W. I. Gerrard, *Brit. med. J.*, ii/1924, 225.

Description of an improved technique for determination of bilirubin in the serum by means of the diazo method. The first improvement is the colorimetric determination in monochromatic light by means of a dimming wire gauze, instead of the fluid for comparison formerly used. This instrument is standardised with azo-bilirubin, derived from chemically pure bilirubin. The second improvement is the prevention of the absorption of bilirubin on the albuminous precipitate which occurred with the old technique. This result is achieved by adding in suitable proportions to the serum a mixture of reagent, diluted alcohol and a buffer.—A. A. H. van den Bergh and W. Grotepass, *Brit. med. J.*, i/1934, 1157.

For older references see previous edition.

Meulengracht Test for jaundice.—*J. Amer. med. Ass.*, ii/1925, 765. *Fouchet Test* for hyperbilirubinemia.—*J. Amer. med. Ass.*, ii/1925, 766. (for full description of test see *C. R. Acad. Sci., Paris*, 1917, 80, 826).

Phenoltetrachlorophthalein. $C_{20}H_{10}O_4Cl_4$. Employed as a test for liver function. Given subcutaneously (in animals) it escapes exclusively *via* the biliary passages. Since the action of the substance itself is purgative, very little absorption takes place. Excretion diminishes in proportion to the amount of liver tissue damage.

Technique. A 5% solution is made by boiling 2.5 g. with 5 ml. of 2N sodium hydroxide and water to 50 ml. The night prior to the test a purgative is given, and on the morning following 8 ml. of the solution is given intravenously.

The stools are collected for 48 hours after. The patient must be purged throughout the test. The fæces are shaken 20 minutes with 1 to 1½ litres of water, and one-tenth of the volume is decanted. 5 ml. of 40% sodium hydroxide is added. The mixture turns red. After thorough shaking, 100 ml. is decanted into a 200 ml. flask containing 5 ml. of saturated basic lead acetate solution, 5 ml. of 40% sodium hydroxide is added and the volume made up to 200 ml. The colour should not be deepened by more soda. The solution is allowed to stand a short time, for the supernatant fluid to clear. In the meantime, a standard solution of the dye is made by taking 0.4 ml. of the original 5% solution, adding sufficient sodium hydroxide to make a permanent colour and water to 1000 ml. Small portions of the two liquids are compared. The percentage recovery of the dye can thus be found. Any recovery below 30% is regarded as pathological.

The test is said to give satisfactory information in advanced cirrhosis, cancer, and syphilis affecting the liver.—Beaumont and Dodds; Rowntree and co-workers.

The test is more delicate than the urobilinuria method and more reliable than the hæmoclastic crisis test, or the lævulose tolerance test, which latter is of little practical value. Thrombosis might be obviated by smaller injection

than that recommended (5 mg. per kilo). Bromsulphthalein similarly employed gives more sharply-cut results.—*Brit. med. J.*, i/1925, 272.

Clinical tests for hepatic function.—C. H. Greene, *J. Amer. med. Ass.*, ii/1925, 476.

Estimation of the phenoltetrachlorophthalein left in the blood after an interval shows that function of the dye is less pronounced with cancer than with cirrhosis. In cases with enlarged liver, retention of dye suggests cancer rather than hepatitis or cirrhosis.—per *J. Amer. med. Ass.*, ii/1925, 1008.

Phenoltetrabromphthalein Sodium Sulphonate, *syn.* **Bromsulphthalein**. 5 mg. per kilo injected intravenously.—S. M. Rosenthal and E. C. White, *J. Pharmacol.*, 1924, 287; *Prescriber*, June, 1925.

It is almost entirely eliminated by the liver, but in cases of retention in the blood stream the dye may be eliminated in the urine from traces up to 20% of the amount injected.—W. J. Kerr and co-workers, *J. Amer. med. Ass.*, ii/1925, 442.

Cases of liver disease show retention of the dye representing the degree of liver damage or functional impairment—100% retention means that no dye is removed from the blood, and 50% that the liver was 50% incompetent, and so on. The test is of liver function and not biliary permeability. It is safe, simple, and appears to be the best.—E. Bulmer, *Lancet*, ii/1928, 326.

Of 20 cases with early liver disease the lævulose tolerance test was positive in 16 while the bromsulphthalein content of the blood serum 5 and 30 minutes after injection showed normal. The 5 minutes' interval retention of the dye does not afford much information in early liver disease, nor does the retention of the dye run parallel with the bilirubin retention.—A. D. Fraser, *Lancet*, i/1928, 654.

Rose Bengal Liver Function Test. Rose Bengal can be either the potassium salt of tetraiodo-di- (or tetra-) chlorofluorescein, or of hydroxytetraiodo-di- (or tetra-) *o*-carboxy-phenylfluorone, or the sodium salt of the two dichloro compounds.

It can be obtained by the action of iodine on dichlorofluorescein in the presence of potassium chlorate and cupric chloride (dichloro compound), or by acting on tetrachlorofluorescein with iodine to produce the tetrachloro body.

It is a dark or brownish-red powder soluble in water without fluorescence.—*Colour Index*, 1924.

Technique. Withdraw sample of blood from vein in the cubital fossa and discharge into graduated centrifuge tube containing 2 ml. of 2% potassium oxalate solution. Without removing needle from vein inject 100 mg. of dye (150 mg. in large persons) in sterile 1% salt solution. Leave needle in vein and 2 minutes after injection withdraw 10 ml. of blood from needle (still *in situ*) into a fresh syringe and discharge into another centrifuge tube containing 2 ml. of oxalate solution: repeat this at 4 and 8 minutes after dye injection. Withdraw needle and leave patient in darkened room for an hour. Centrifuge blood samples at 2000 revs. for $\frac{1}{2}$ hour, and note percentage of cells and plasma in each tube. From the last three samples dilute 3 ml. of plasma in separate tubes with an equal volume of salt solution and compare the colours in a Hellige colorimeter with standard solution containing 5 ml. plasma from first tube and 1 ml. of 0.0075% solution rose bengal. The colorimeter reading is corrected to allow for the 2 ml. oxalate solution. Having obtained the concentration of the dye in the 2-minute sample, and knowing the total amount of dye injected, calculate the blood volume of the person. For the purposes of comparison, a standard blood volume of 7000 ml. is taken, and the final concentration is obtained by multiplying the corrected reading by the blood volume and dividing by 7000.

The dye is eliminated almost entirely from the blood stream through the liver. It remains in the circulation for a sufficient length of time for determination of the dye in the plasma to be made. Patients with definite cirrhosis or other extensive liver disease show marked retention of the dyes in the blood. The test may be of great value when jaundice and ascites are presenting symptoms. Technique described.—W. J. Kerr and co-workers, *J. Amer. med. Ass.*, i/1925, 946. See also i/1927, 1620.

Sodium Salicylate as Liver Test. Normally, the liver transforms $2\frac{1}{2}$ grains, so that none is found in the urine by ferric chloride during 5 hours following the dose. A violet ring at zone of contact indicates inefficient function. Give the dose 1 hour after breakfast.—*Yearb. Pharm.*, 1925, 63.

CALCULI

Urinary Calculi. The size and shape of urinary calculi depend on the region of the urinary tract in which they form. Their chemical composition depends on the character of the urine in which they form. Since the urine may frequently change its character during the slow growth of the stone the end result is usually a laminated calculus with layers of different colour, consistence and chemical composition. There may or may not be an organic nucleus to the calculus. Changes in the reaction of the urine are primarily responsible for the progressive growth of the calculus, increasing acidity causing uric acid to deposit and increasing alkalinity causing deposition of phosphates and urates. It is probable that many calculi centre round a primary uric acid infarct of the tubules of the kidney. The chief secondary changes produced by a calculus are hæmorrhage, infection, and the deposition of organic elements round the stone. The commonest varieties of urinary calculi are the calcium oxalate, uric acid, ammonium urate and phosphatic calculi.

Calcium oxalate stones are extremely hard, usually round and distinguished by their dark brown colour and by their rough "mulberry-like" exterior. They are often formed around a nucleus of uric acid or urates. The irritation caused by the rough surface leads to the deposition of carbonates and phosphates which may fill up the depressions and smooth off the surfaces.

Phosphatic calculi have a rough white crumbly surface. They form when the bladder is inflamed and consist chiefly of ammonio-magnesium phosphate and calcium phosphate.

Uric acid calculi are smooth and hard, like pebbles. The centre may contain a granule of ammonium urate round which fine delicate yellow laminæ are regularly laid down. A pure uric acid calculus may not show by X-rays because its permeability is practically the same as surrounding soft tissues but mixed calculi composed of uric acid with calcium phosphate or oxalate may be recognised radiologically.

Cystine. Calculi containing cystine are usually fairly pure but occasionally they are found with a superficial phosphate coat. They are rare.

Xanthine as a urinary calculus is extremely rare.

Chemical Examination of Urinary Calculi.

If possible a representative sample should be analysed either by examination of half a powdered calculus or by examination of the individual layers. When the preservation of the stone is important it is best to use the powder obtained from a boring to the centre.

Preliminary Examination. Heat a small portion of the powder on platinum foil. This will show if the bulk of the calculus is chiefly organic or contains high proportion of ammonium salt. The presence of cystine will be shown by blue flame and a pronounced mercaptan-like odour. All calculi contain proportion of organic matter.

Platinum Wire Test. Heat a small portion of the powder in a platinum wire loop in a burner flame and after moistening with a drop of concentrated HCl again heat in the flame. Calcium which has been present in the original powder

oxalate or carbonate will yield a brick-red flame. Calcium phosphate will not give a flame but when the powder is first heated in the platinum wire the calcium oxide from calcium oxalate and calcium carbonate will give a limelight effect. Calcium phosphate will remain as an infusible white powder and ammonio-magnesium phosphate will melt and run into a bead.

To decide if a calculus consists chiefly of uric acid and phosphate or oxalate the following solubility test is useful. Boil a small amount of the powder with 10% HCl. This will dissolve all except uric acid. The insoluble uric acid will be found to be readily soluble in a solution of lithium carbonate. Confirm by applying murexide test to the original powder. Flocculent organic debris should not be mistaken for the insoluble uric acid. To the filtrate from the above add concentrated ammonia until there is a slight excess. Any precipitate will be due either to phosphate or oxalate. Add glacial acetic acid until there is slight excess. Phosphate will dissolve, calcium oxalate will be insoluble. Confirm calcium oxalate by flame test and phosphates by molybdate reaction. Cystine would be precipitated from the ammonia solution by the acetic acid. Confirm by lead test or by seeing characteristic hexagonal crystals microscopically.

Murexide test for presence of uric acid. Heat a pinch of the original powder in an evaporating dish with 3 or 4 drops of concentrated nitric acid. A red colour develops. A drop of 40% sodium hydroxide will give a mauve colour.

Molybdate test for phosphates. Warm a pinch of the original powder with a few drops of concentrated nitric acid in a test-tube, add 3 to 4 ml. of 10% ammonium molybdate and warm. A canary yellow colour and precipitate will form if phosphates are present.

Lead test for cystine. Boil a pinch of powder with 3 to 4 drops of solution of lead acetate and 5 to 6 drops of 20% sodium hydroxide. A black precipitate of lead sulphide will form if cystine is present. Ammonia may be detected in the calculi by boiling a pinch of the powder with 20% sodium hydroxide. The ammonia may be recognised by its odour or by litmus paper.

Biliary Calculi (Gall Stones). Concretions forming in the gall bladder and bile ducts. Large gall stones generally consist almost entirely of cholesterol with some bile pigments. Smaller stones contain a higher proportion of bile pigments and calcium, while very small calculi composed of bile pigment only occur. Calculi found in the common bile duct often contain a high proportion of fatty acids.

Cholesterol. The cholesterol content of the blood is no guide to the possibility of the presence of gall stones.

Cholesterol content of blood serum after irradiation with X-rays.—*Brit. med. Abstr. A.*, 1928, 1152.

Hypercholesterolaemia possessing the "nephrotic" syndrome, marked by diffuse parenchymatous degeneration, heavy albuminuria, changes in the plasma protein, and with oedema as the chief symptom. It is not found in interstitial nephritis, arteriosclerotic kidney, or arteriosclerosis. In myxoedema the total cholesterol of plasma may be increased by nearly 50% above normal. Cholesterol metabolism in disease.—J. A. Gardner, *Brit. med. J.*, ii/1932, 392.

CASTS

The presence of casts may be an important indication of renal disease. The centrifuged deposit is examined both with the 1/3 and later with the 1/6 inch objective. Casts have a sharp outline. Their significance depends on their character.

Cellular casts may be composed of red blood corpuscles, pus cells or the mononuclear cells of renal epithelium, and indicate acute nephritis. In chronic parenchymatous nephritis and in acute nephritis after the first few days of the disease the casts are usually granular, and represent a later stage of the cellular casts which have undergone a granular degeneration.

Hyaline casts, with structureless contents, may be found in any form of nephritis but are commonest in chronic interstitial nephritis and hyperpiesia. A few hyaline casts may be present in the urine of healthy people.

Cylindroids are pale ribbon-like bodies with tapering ends which are found in inflammations of the urinary tract.

CHLORIDES

Instead of evaporating and incinerating with ammonium nitrate, oxidise the organic matter contained in 10 to 20 ml. of urine by warming with 3 ml. of sulphuric acid and a slight excess of potassium permanganate solution. The addition of a few drops of hydrogen peroxide will then cause the precipitated manganese dioxide to dissolve giving a clear solution. To this add a few ml. of nitric acid and a measured excess of N/10 silver nitrate solution, boil and cool. After adding 1 or 2 ml. of ferric alum solution to the mixture, titrate the excess of silver with N/10 ammonium thiocyanate.

CHYLE

Chyle gives to urine a milky appearance due to the presence of an emulsion of fat which sometimes separates on standing. The urine is acid, with sp. gr. usually between 1·015 and 1·020; it is coagulated with nitric acid, contains 0·6% to 0·9% of protein, 0·8% to 1·8% of fat, about 1·5% to 2% of urea, and no sugar. Often the fat emulsion is so fine that no creaming occurs on standing. The fat may be removed by shaking with ether but the shaking must be prolonged. Chyluria is usually due to rupture of lymphatics in the bladder wall due to an obstructive condition in the pelvis. Sometimes the condition diagnosed as chyluria is really due to chyle passing *per vaginam* becoming mixed with the urine.

Sudan III Test of True Chyluria. 100 mg. of Sudan III is given in 10 g. of butter. Normally no dye will appear in the urine. In chyluria the urine will be pink owing to the dye remaining attached to the fat excreted in the urine.

CREATININE

Glycocoll-methylguanidine. $C_4H_7N_3O$. To test for this body in the urine add a little sodium nitroprusside and caustic soda. A red colour develops which fades on boiling the mixture. If a little acetic acid is added to the boiling liquid prussian blue is produced.

Creatinine, creatine and mucin have a retarding effect on the precipitation of cuprous oxide from Fehling's solution. Urates have an auxiliary effect.

Excretion of creatinine in diabetes mellitus. There appears to be some connection between carbohydrate metabolism and the creatine-creatinine metabolism. Experiments with diabetic urines showed that creatinine was not increased to any extent even when patients were on a highly nitrogenous diet. Creatine on the other hand is a substance never found in the normal urine if the diet is free from creatine, and creatinine was always found—even when patients were on a creatine-creatinine-free diet.—*Brit. med. J.*, ii/1910, 1343.

Creatinine and creatine in blood. Method of estimation by means of the **Hellige colorimeter**. See *Blood and Urine Chemistry*, Gradwohl and Blaivas, 1920.

CYSTINE

Cystine, $(S \cdot CH_2CH \cdot NH_2 \cdot COOH)_2$, is a cleavage product of protein metabolism, apparently loosely bound and easily split off at an early period of the intestinal digestion. Normally it becomes oxidised and hence is unrecognisable but in cystinuria it is excreted unchanged.

Separation of cystine. Free from oxalates and phosphates by ammonia and subsequent addition of calcium chloride until this no longer precipitates, add

ual volume of acetone and acetic acid in slight excess. Cystine crystallises in 3 or 4 days, and may be purified by dissolving in ammonia and reprecipitating.—Mann.

It is occasionally found in urinary deposits as transparent six-sided crystals—insoluble in alcohol but soluble with ease in mineral acids and ammonia. Cystine is insoluble in dilute acetic acid. Uric acid occasionally crystallises in similar form, but gives the murexide reaction; cystine does not.

FORMALDEHYDE

Martindale conducted some examinations of urine for formaldehyde to determine whether excretion of formaldehyde occurs after administration of hexamine and allied bodies (cf. Hexamine, Vol. I and this vol.). The following tests were found of service:—

Phloroglucin Test. To 5 or 10 ml. of sample add 5 drops of 1% aqueous solution of phloroglucin followed by 5 drops of 30% caustic soda solution. A red colour appears if formaldehyde is present. Will show 1 in 2,000,000 of water and 1 in 50,000 of urine. Shows no colour with hexamine.

Rimini's Test. To 5 or 6 ml. of sample add 1 drop of 1% aqueous solution of phenylhydrazine, then 1 drop of 1% aqueous solution of sodium nitroprusside and 5 drops of 30% caustic soda solution. Blue colour appears if formaldehyde is present. Will show 1 in 100,000 of urine; shows no colour with hexamine; in 150,000 of urine can be seen.

'Meta' Test (Martindale). To 10 ml. of sample add 0.05 ml. of 5% aqueous solution of *m*-diaminobenzene hydrochloride. Gives a yellow colour or precipitate if formaldehyde is present. Will show 1 in 20,000 of water by colour and 1 in 2 in 10,000 of urine by opalescence or precipitate. Gives no reaction with hexamine.

GLUCOSE

The absorption, circulation and utilisation of sugar depend on the harmonious activity of many different organs of the body and glycosuria may result from the breakdown of this co-operative activity at different points. It is most important to remember that glycosuria does not necessarily indicate diabetes. It is only after the exclusion of the less serious causes of glycosuria that a diagnosis of diabetes is justified. The bulk of carbohydrate is absorbed from the intestine in the form of glucose. This travels to the liver via the portal circulation. Part is stored in the liver and part in the muscles as glycogen. The speed and efficiency of storage is reflected in the blood sugar and is controlled by the insulin of the body. A lack of insulin means delayed or partial storage and a correspondingly high blood sugar. When the blood sugar reaches a certain level, sugar will appear in the urine.

Alimentary glycosuria results when sugar is absorbed from the intestine more quickly than it can be stored, so that the blood sugar rises and the leak point is passed. This is not a common occurrence, and experiments have shown that it is difficult to produce alimentary glycosuria in healthy individuals even after consumption of enormous quantities of sugar.

Renal glycosuria results when the leak point of the kidney is set at a lower figure than normal. Thus some individuals excrete sugar in the urine even when the blood sugar is only 100 mg. per 100 ml. In such people glycosuria appears after a carbohydrate meal when the blood sugar is likely to rise. Renal glycosuria is an innocent condition, but it is advisable to keep such patients under observation.

Endocrine glycosuria occurs in hyperthyroidism, pituitary tumours and after injections of adrenaline. The hormones here involved probably act by stimulating the liver to break down glycogen, with the result that hyperglycæmia and glycosuria result.

Injuries to the floor of the fourth ventricle cause sugar to appear in the urine, and this has been described as **nervous glycosuria**. The probable explanation is that injuries to this region of the brain cause a stimulus to the suprarenals with an increase in the adrenaline in the blood, and therefore an adrenaline glycosuria.

True diabetes results from the inability of the tissues to utilise carbohydrate, owing to the absence of insulin provided by the pancreas. This inability to utilise carbohydrate is interpreted by the body as a stimulus for the production of more glucose so that all available carbohydrate is poured into the blood, producing a hyperglycæmia. Since the tissues cannot utilise the sugar it is excreted in the urine.

These different forms of glycosuria can be distinguished by estimations of the blood sugar and observation of the glucose tolerance test.

Benedict's tests for sugar in urine are those most commonly used. They are simpler and avoid the fallacies of Fehling's test.

Benedict's Quantitative (Modified Fehling) Test. Copper sulphate 18 g., sodium carbonate cryst. 200 g., sodium citrate 200 g., potassium sulphocyanide 125 g., 5% potassium ferrocyanide solution 5 ml., water to 1 litre. The test is as Fehling's—the end-point being disappearance of the blue colour.

To conduct the test 25 ml. of the reagent is measured into a small flask and about 4 g. of anhydrous sodium carbonate added and the solution brought to the boil. Urine is then run in slowly from a burette until the reagent turns from clear blue to an opalescent bluish-white colour, when the additions are made more carefully until the colour disappears. This gives a rough indication of the amount of sugar in the urine and the titration is repeated after first diluting the urine so that about 10 ml. will reduce the reagent. 25 ml. of the reagent is reduced by 0.05 g. of glucose. This quantity is therefore in the volume of urine reducing 25 ml. of the reagent.

Benedict's Qualitative Test. Dissolve with heat sodium (or potassium) citrate, 173 g., and 100 g. of anhydrous (or 200 g. cryst.) sodium carbonate in water, about 700 ml. Dissolve separately pure crystallised copper sulphate, 17.3 g., in water about 100 ml. Cool to room temperature, pour the second into the first solution slowly with stirring and make up to 1000 ml. with distilled water.

The patient can employ the test himself. 5 ml. is boiled with 8 drops of urine for two minutes and cooled. If glucose is present the colour changes to an opalescent green, or, in the case of a large quantity of sugar, to an opaque red. Benedict's reagent is reduced

by glucose, lævulose, lactose, pentose and homogentisic acid, but not by uric acid and creatinine.

To confirm and distinguish glucose employ the fermentation test, (see p. 323).

Benedict's qualitative reagent may be used in a rough quantitative way using 0.25 ml. of urine and 5 ml. of the reagent.

A green opalescence = between 0.12% and 0.5%.

A green precipitate = 0.5% to 1.0%.

A yellow precipitate = 1.0% to 2.0%.

A red precipitate = Over 2.0%.

These only apply to the appearance immediately after the boiling and not to what may occur on standing.

FURTHER TESTS AND REAGENTS FOR GLUCOSE

Fehling's Solution (Potassio-cupric Tartrate Solution)

Glucose, being an aldehyde, has a strong reducing action. In the test the alkaline glucose-cupric oxide, when heated, causes deposition of cuprous oxide. 1 molecule of glucose reduces practically 5 molecules of cupric oxide.

In making use of Fehling's solution it is important when looking for small quantities of sugar to dilute the urine to about sp. gr. 1.015. Mix with an equal volume of mixed Fehling's solution. Boil for a few seconds—if no precipitate within two minutes there is no sugar of pathological import.

Great care, however, should be taken not to confuse with reducing substances other than glucose.

Fehling's Solution is prepared in two solutions:—No. 1. Copper sulphate 34.64 g., sulphuric acid 0.5 ml., distilled water to 500 ml.

No. 2. Sodium hydroxide 77 g., sodium potassium tartrate 76 g., distilled water to 500 ml.

Mix equal volumes when required. Of this, 10 ml. will be decolorised and reduced by 0.05 g. (or 53 minims by $\frac{1}{4}$ grain) of glucose or diabetic sugar in solution, with precipitation of yellowish-red cuprous oxide when the two are boiled together. No. 2 solution should not be kept in a very cold place or it may crystallise. By keeping the copper solution separate from the alkaline solution the test is prevented from becoming erroneously sensitive.

A little calcium carbonate or barium sulphate greatly assists the deposition of the cuprous oxide and enables the colour of the supernatant liquid to be more easily seen.

On p. 321 is given a table showing equivalents in glucose when using **Gerrard-Fehling solution**. The figures there given apply exactly as if 10 ml. of Fehling's as used in place of the Gerrard's solution.

Sterules, containing 1 ml. of Fehling's solution, are available.

Glucose ★ Endolytic Tubes are prepared—use similar to those for albumin

v. The reaction may be obtained in the cold or by pouring boiling water on to the charged tube (sealing is not necessary). Or, indeed, if not available, a lighted match drawn carefully along the tube will suffice. If done in the cold, the sealed tube should be inspected for the usual cuprous oxide precipitate after 12 to 24 hours.

Fehling's is reduced by dextrose, lævulose, mannitose, milk sugar, galactose, arabinose, aldehyde, formaldehyde (see below), chloral, chloroform, creatinine, valeraldehyde, resorcinol, pyrogallol, gallotannic acid, arsenic trioxide, and similar reducing bodies, glycosides, and acetone: also by glycuronic acid, uric acid, pyrocatechin, hydroquinone and salicylic acid compounds; these may be removed by simple repeated filtration through animal charcoal. None of these bodies ferments or gives osazone crystals. *Vide* phenylhydrazine tests.

An orange precipitate formed when hot urine is mixed with hot Fehling's solution without reboiling affords almost conclusive evidence of the presence of hexose monosaccharide such as glucose or lævulose.

An orange precipitate formed on boiling is sometimes due to the presence of a compound glycuronate.

To make certain of glucose the urine must contain a + **rotatory reducing** substance, fermented by yeast (both glucose and lævulose are), it must yield an osazone of the correct crystalline form, melting at slightly above 200° (both glucose and lævulose give this) and finally it must yield no osazone in case of glucose with methylphenylhydrazine, which, with lævulose, yields one melting at 150°.—A. E. Garrod, *Lancet*, i/1912, 484.

Tollen's Test for glycuronates consists in boiling the urine for one minute with an equal volume of concentrated hydrochloric acid and a small quantity of a solution of naphthoresorcin in alcohol. After cooling and shaking with ether the ether layer will be coloured violet to red if glycuronates are present.—F. Wokes, *Pharm. J.*, ii/1925, 127.

Uric Acid and Urates in the presence of oxalates and biphosphates reduce Fehling's (*Yearb. Pharm.*, 1927, 94) but uric acid does not introduce any great error by its reduction of Fehling's solution. Experiments showed that 1% uric acid completely reduced an equal volume of Fehling's with about one minute's boiling. There was a slight reduction with 0.1% solution with Fehling's but none with Nylander's reagent. 10 ml. Fehling's (=0.05 g. of glucose) by Gerard's process required 14 ml. of 1% uric acid (=0.14 g.), which would be equivalent to 250 ml. of normal urine approximately, which would = 0.02% + error in estimating glucose, *i.e.*, the amount is negligible. Consequently uric acid does not hinder the reduction of Fehling's solution by glucose.

Formaldehyde also reduces Fehling's and should not be used to preserve urines for examination as to diabetes. If in doubt as to the presence of formaldehyde boil with excess of strong ammonia solution before conducting Fehling's test. Another reason for refraining from its use is that formalin combines with urea, forming crystals not unlike leucine on the side of the container.

Lloyd's Reagent (ALUMINIUM SILICATE) removes interfering substances.

To 5 ml. of urine add 5 ml. of N/10 sulphuric acid and 10 ml. of water. Add 1.5 g. of Lloyd's alkaloidal reagent and shake gently for 2 minutes. This removes most of the colouring matters, uric acid, creatine, creatinine, yet unlike charcoals, does not take away the sugar. (It is not necessary to remove even trace of creatinine). Filter. 2 ml. used for the usual colorimetric sugar determination. Shaking should not be continued for longer than 2 minutes, as acid gradually dissolves the reagent—the dissolved aluminate does not, however, interfere. With more dilute urines, use 10 to 15 ml. For total sugars invert 10 ml. of above filtrate by heating in boiling water for 75 minutes with 1 ml. 10% of hydrochloric acid. Cool, neutralise to phenolphthalein, dilute to 20 ml., add a small pinch of Lloyd's reagent, shake, and immediately filter. Take 2 ml. for determination. Dilute sugar standards found to keep perfectly in 0.3% benzoic acid solutions.—Otto Folin and Hilding Berghund, *J. biol. Chem.*, 1922, 51, 209.

The reagent also adsorbs alkaloids in acid solution. These adsorbed alkaloids are liberated and regain their previous solubility in alkaline solutions.—*Brit. chem. Abstr.*, 1913, 2663.

TRICHLORACETIC ACID does *not* reduce Fehling itself, but tends to inhibit the reduction by sugars, so that *quantitative* results cannot be obtained in its presence.

Reducing substances in the urine; their detection and identification.—J. P. Bose, *Indian med. Gaz.*, 1926, 173.

Fehling's is not reduced by mannite, dulcitol, sucrose, inositol, cellulose, dextrin, arabin, alcohol, glycerin, phenol, benzaldehyde, salicyl aldehyde, acetic, lactic, oxalic, succinic, tartaric, citric, gallic, saccharic, mucic, gluconic, benzoic, salicylic and sulphurous acids, and alkaloids.

Allen's Modification of Fehling's Test. For small quantities of sugar in urine. Heat 8 ml. of the urine to boiling-point and add 5 ml. of the copper solution, cool and add 2 ml. saturated solution of sodium acetate, slightly acidified with acetic acid, to complete precipitation of uric acid, phosphates, and xanthine. After, add 5 ml. of the alkaline solution, and boil for a few seconds. If more than 0.25% of sugar be present, cuprous oxide is precipitated before boiling-point is reached, but if less than this proportion, it is deposited during cooling.

Gerrard's Solution. This is prepared by diluting 100 ml. of mixed Fehling's solution with about 300 ml. of water and almost decolorising, whilst boiling, with 5% solution of potassium cyanide (using good commercial cyanide, about 10 ml. are required), and making up the volume when cold to 500 ml.

Method of use. Mix 50 ml. of the solution with 10 ml. of mixed Fehling's solution (5 ml. Fehling's No. 1, and 5 ml. Fehling's No. 2). Boil in a basin and pour into it, whilst boiling, diluted urine, $\frac{1}{2}$ to 1 ml. at a time, by means of a pipette, until the blue coloration just disappears, taking care not to add an excess. An average diabetic urine may be diluted 1 to 10 with water.

The number of millilitres of actual undiluted urine used contains 0.05 g. of glucose. From this the percentage—grammes per 100 ml.—is easily obtained. To convert this into grains per fl. oz. multiply by 4.375. The product multiplied by 20 gives the number of grains per pint. The following table will be found useful:—

No. of ml. of diluted urine used	g. of sugar per 100 ml.	Grains per fl. oz.	Grains per pint	No. of ml. of diluted urine used	g. of sugar per 100 ml.	Grains per fl. oz.	Grains per pint
4.0	12.5	54.69	1093.80	3.0	3.30	14.45	289.00
4.5	11.1	48.56	971.20	3.5	2.90	12.70	254.00
5.0	10.0	43.75	875.00	4.0	2.50	10.95	219.00
5.5	9.1	39.86	797.20	4.5	2.20	9.64	192.80
6.0	8.3	36.35	727.00	5.0	2.00	8.76	175.20
6.5	7.7	33.73	674.60	5.5	1.80	7.88	157.60
7.0	7.1	31.10	622.00	6.0	1.70	7.45	149.00
7.5	6.7	29.35	587.00	6.5	1.50	6.57	131.40
8.0	6.3	27.59	551.80	7.0	1.40	6.13	122.60
8.5	5.9	25.84	517.80	7.5	1.30	5.69	113.80
9.0	5.6	24.97	499.40	8.0	1.25	5.49	108.80
9.5	5.3	23.21	464.20	8.5	1.18	5.17	103.40
10.0	5.0	21.90	438.00	9.0	1.11	4.86	97.40
10.5	4.8	21.02	420.40	9.5	1.05	4.60	92.00
11.0	4.5	19.71	394.20	10.0	1.00	4.38	87.60
11.5	4.3	18.83	376.60	10.5	0.95	4.15	83.00
12.0	4.2	18.40	368.00	11.0	0.91	3.96	79.20
12.5	4.0	17.52	350.40	11.5	0.87	3.81	76.20
13.0	3.8	16.61	332.20	12.0	0.83	3.64	72.80
13.5	3.7	16.21	325.20	12.5	0.80	3.50	70.00
14.0	3.6	15.77	314.40	13.0	0.77	3.37	67.40
14.5	3.4	14.86	297.20	13.5	0.74	3.24	64.80
				14.0	0.71	3.11	62.20
				14.5	0.69	3.09	61.80
				15.0	0.67	3.00	60.00

The four columns on the right give the results with the urine diluted with an equal volume of water. If the urine contains less sugar than this, employ it undiluted. The calculation is then as before: the number of millilitres of actual urine used contain 0.05 g. of glucose.

Trommer's Test. To 5 ml. of urine add $\frac{1}{2}$ vol. of 15% sodium hydroxide and then 1 ml. of 10% copper sulphate solution. A red or yellow precipitate appears on standing in the cold a few hours or more rapidly on boiling. On heating, much of the cupric hydroxide may remain undissolved—an excess of alkali is necessary as in the case of Fehling's solution (or less copper solution can be used). Fehling's test has superseded Trommer's. They are employed in the same manner. Trommer's test may be interfered with by creatinine. It is important to add the alkali before the copper solution.

Barfoed's Reagent. Neutral copper acetate 13·3, acetic acid solution (1% 200. A glucose solution warmed with a small quantity of this precipitates cuprous oxide.

An improved form contains copper acetate 50, sodium acetate 50, glacial acetic acid 5, water to 1000. With this, reduction is obtained with 0·1% dextrose solutions on merely heating to boiling, while 1% solutions of maltose or lactose do not show reduction under similar conditions.—*J. chem. Soc. Abstr.*, ii/1925, 525.

Nitropropiol. Sodium *o*-Nitrophenylpropiolate. $C_9H_4Na(NO_2)O_2$. Owing to reduction, indigo blue colour is produced, or indigo blue itself precipitated. This reaction is based upon Bayer's synthesis of indigo blue which is briefly:—Cinnamic acid \rightarrow orthonitrocinnamic acid \rightarrow dibromide compound \rightarrow orthonitrophenylpropionic acid, which, warmed with alkali in the presence of glucose decomposes thus:— $2C_9H_5(NO_2)O_2 = C_{16}H_{10}N_2$ (indigo blue) + $2CO_2 + O_2$. This substance is to be distinguished from sodium phenylpropiolate.

Sodium *o*-nitrophenylpropiolate solution is employed of the following composition: Place 5 g. of *o*-nitrophenylpropionic acid in a mortar and wash alternately with 1 to 2 ml. of water and 1 to 2 ml. of 10% sodium hydroxide solution until dissolved (altogether about 8 to 10 ml. required). Dilute to 1 litre. On boiling 5 ml. with 1 ml. of urine the blue colour of indigo appears either immediately or in 30 seconds according to amount of glucose.

Nylander's Reagent. Bismuth subnitrate 2, Rochelle salt 4, sodium hydroxide solution (8%) 100; and **Almen's reagent** consisting of bismuth subnitrate 2, Rochelle salt 2, potassium hydroxide solution (35%) 50, are used for detecting glucose. The reagents should be stored in bottles of actinic glass. A small quantity of either when warmed with the urine will blacken it if glucose be present.

This reagent is not interfered with by the presence of uric acid. Even a 1% solution of the acid does not produce any appreciable reduction on boiling for 5 minutes.

Cramer's Mercury Test. Dissolve mercuric oxide (red or yellow) 0·1 g. with potassium iodide 6, in water 100 and adjust the alkalinity of the solution so that 10 ml. is neutralised to phenolphthalein by 2·5 ml. of N/10 acid.

To use the test heat 3 ml. of the solution to boiling, add 0·3 ml. of urine and boil again. On removing from flame the mixture darkens if sugar is present. Metallic mercury settles ultimately. Glucose, lactose, maltose, xylose and arabinose give the reaction, but not cane sugar.—*Biochem. J.*, March, 1915, per *Lancet*, i/1915, 1192. The test is quite sensitive. The deposit of metallic mercury is of greyish colour.

Osazone Reaction. Phenylhydrazine hydrochloride is used as a test for sugar. It is in colorless, shining, crystalline scales, and should be free from azo-compounds. As much as will cover a sixpence is dissolved with twice its quantity of sodium acetate in about 1 ml. of glacial acetic acid. To this is added 10 ml. of urine. If the solution is not clear after well mixing it should be filtered. The filtrate is placed in a tube in a boiling water-bath for 30 minutes. The water-bath should then be allowed to cool with the tube still in it so that the very slow cooling will help the formation of characteristic crystals. The crystals form in yellow sheaves or clusters.

This substance should be handled with care since it may produce eczema. Boil 2 to 3 ml. of the urine with an equal quantity of water and phenylhydrazine hydrochloride 0·1 g. and sodium acetate 0·5 g. Add 10 ml. of sodium hydroxide 10% solution, invert test-tube a few times and allow to stand. A pink to red colour of the whole liquid in 5 minutes indicates sugar of clinical significance.

Osazone Reaction in Health. Urines from more than 700 sources show that 20% to 30% voided 1 to 2 hours after an ordinary meal yielded typical glucosazone crystals, the percentage dropping to 12 to 15 in urines passed 4 to 5 hours after meals.—*Brit. chem. Abstr.*, 1928, 1273. For earlier refs. on this matter see *Edn. XVIII, Vol. II*, pp. 409, 410.

Picric Acid. Johnson's or Braun's Test. This has been suggested as a test for glucose in urine, since a solution of this sugar, if boiled with picric acid and solution of potash, reduces the yellow picric acid to the deep red picramide acid, forming potassium picramate, the depth of colour depending on the amount of sugar. By the aid of Johnson's Picro-Saccharometer this reaction can be made quantitative. Solution for use with same: strong solution of ferric acetate

B.P. '85) 15 drachms, glacial acetic acid $7\frac{1}{2}$ oz., ammonia solution 0.959, $\frac{3}{4}$ oz., water to 3 pints.

Safranin Solution. 1 in 1000. One volume of this, with one of urine and one of solution of potash is heated to boiling, avoiding agitation. If the urine contains sugar to the extent of 0.1% the liquid will be decolorised. (On cooling, the colour may return in proportion to the amount of sugar present.) Each additional volume of the safranin solution that may be decolorised represents roughly 0.1% of sugar.

Safranin solution (unlike Fehling's solution) is unaffected by creatine, creatinine, uric acid and urates. The test deserves to be better known.

Phosphomolybdic Acid. For estimating normal urinary sugar. Toluene is useful to preserve. 1 ml. of specimen is precipitated by 2 ml. of phosphotungstic acid reagent made of 2% phosphotungstic acid in 5% sulphuric acid. A dense precipitate is formed. After thoroughly shaking, dilute to 10 ml. by adding 7 ml. of distilled water; shake and filter. This filtrate is clear and free from creatinine and other interfering substances. 1 ml. of the liquid is heated 5 minutes in a boiling water-bath with 2 ml. of alkaline copper solution. Remove and add phosphomolybdic acid solution. Presence of sugar is shown by a deep blue colour. This can be made colorimetric by comparison with a glucose solution. The amount normally present is very constant. It exceeds 1 g. a day on ordinary mixed diet, and the percentage in the urine corresponds curiously closely with that regarded as normal in blood, namely, 0.08% to 0.1%.—R. L. Mackenzie-Wallis, *Lancet*, ii/1921, 1003.

Dinitrosalicylic Reagent for colorimetric determination of sugar prepared as follows. To 10 g. of phenol add 22 ml. of 10% sodium hydroxide and make up to 100 ml. Add 69 ml. of this solution to 6.9 g. of sodium bisulphite and mix with 300 ml. of 4.5% sodium hydroxide, 255 g. of Rochelle salt and 880 ml. of 1% dinitrosalicylic acid solution.

To 1 ml. of urine add 3 ml. of reagent, heat for 5 minutes in boiling water, cool and dilute to 25 ml. Compare with standards containing 1, 0.5, and 0.25 mg. of glucose. Concentrated urines containing over 0.18%, and dilute urines containing over 0.12% of sugar, can be considered abnormal.—J. B. Sumner, *J. biol. Chem.*, 1925, 65, 393.

Fermentation Test. A useful confirmatory test. Prior to conducting, determine the specific gravity of the urine as exactly as possible. Then fill a Woburn tube completely with the specimen; place a little fresh yeast in the end; keep in a moderately warm position for 24 hours. If sugar is present, carbon dioxide will be produced, and the gravity of the urine will fall—each degree of density lost being equivalent approximately to 1 grain of glucose per ounce.

Roberts' Method. After complete fermentation, compare with the original sp. gr.; a decrease of 0.001 in the sp. gr. corresponds to 0.23% of sugar. When the sugar content is not less than 0.4% to 0.5%, and the readings are carefully taken at the same temperature, the method gives fairly exact results.—*Chem. & Drugg.*, 1921, 72.

Fungi in Relation to Human Pathology. The "Yeast Method" of detecting glucose in urine is not specific. Ordinary samples of baker's yeast will ferment levulose, maltose, galactose, saccharose, lactose, and other carbon compounds in addition to glucose. (This difficulty can be overcome by washing and filtering the yeast and by putting up suitable control tests against known solutions of glucose which is the commonest cause of doubt.—Archer). A germ should be used which ferments glucose only, e.g., *Monilia balcanica* Castellani, or, failing this, *Monilia Krusei* Castellani, which ferments glucose and levulose only.

A mycologic method described especially useful for identification of maltose and galactose.—A. Castellani and F. E. Taylor, *J. trop. Med. (Hyg.)*, 1926, 209. See also A. Castellani, *Lancet*, i/1920, 847, 895, and P. Pietra, *J. trop. Med. (Hyg.)*, 1927, 182.

Renewed investigation of the normal urine sugar problem has brought forth challenges of the presence of glucose. Lund and Wolf of Addenbrooke's Hospital, Cambridge, proceeded from the thesis that if glucose is present in urine the products of its fermentation should be detectable when this reaction is attempted, but the most delicate tests failed to demonstrate production of carbon dioxide when normal urine was treated with yeast, pointing clearly to the absence of glucose from normal urine.—*J. Amer. med. Ass.*, ii/1925, 1308.

Carbohydrate Test. The char is most distinctive of a saccharine urine.—Barker Smith, *Pharm. J.*, ii/1924, 309; i/1925, 100.

LÆVULOSE

Lævulose reduces Fehling's solution, ferments with yeast and forms an osazone with phenylhydrazine like glucosazone. Occasionally found in urine alone—more commonly with dextrose.

Pseudo-lævulose of diabetic and other urines. True lævulosuria or fructosuria may be met with, but it is apparently rare. The lævorotatory body is in reality the ketonic acid isoglycuronic acid, which is differentiated from lævulose by Borchardt's test—the acid is precipitated from an acid solution on saturation with lead acetate—and the melting-point of the parabromphenylosazone. Specimens from 30 cases of so-called lævulosuria and 50 of diabetes, in which a lævorotatory substance was present along with dextrose, were examined and in none could any true lævulose be found.

Borchardt's Modification of Seliwanoff's Test consists in treating the specimen with hydrochloric acid and resorcinol, making alkaline with sodium carbonate and extracting with ethyl acetate. With *plant* lævulose the extractive is red in colour, but with urines giving the ordinary Seliwanoff reaction the watery solution retains the pigment and the extract is yellow.—P. J. Cammidge and H. A. H. Howard, *Lancet*, i/1915, 320.

Seliwanoff's Reaction for Lævulose. On warming a solution of resorcinol in 1 part of concentrated hydrochloric acid and 2 parts of water with lævulose an intense red coloration is formed and gradually a dark precipitate soluble in alcohol with production of a red colour. Glucose, lactose, maltose and pentose do not give this colour. Glucose will give a positive reaction if the boiling is prolonged.

Seliwanoff's Reaction for Cane Sugar. The test applied exactly as above gives only a very faint pink on warming. Takes some minutes to form. Using strong hydrochloric acid, the reaction for both is the same. The precipitate in both cases is soluble in alcohol.

HIPPURIC ACID

Hippuric acid is excreted daily to the extent of about 0.5 to 1 g. on a mixed diet or it may reach 2 or 3 g. on a vegetarian diet. It is formed by the interaction of dehydrated benzoic acid and glycocoll in the system. Protein in the intestines produces amino acids which are oxidised to benzoic acid. **Glycocoll** is a normal product of metabolism, and by this reaction renders the benzoic acid (*inter alia*) harmless; this occurs, it is thought, in the kidneys.

1 of the free acid in 55,000 of water will change congo red paper to blue, but urine does not cause the change—showing that the hippuric acid present is in the combined condition.

Hippuric Acid Estimation. Heat 100 ml. of urine with 10 g. sodium hydroxide in a Kjeldahl flask with reflux condenser for $2\frac{1}{2}$ hours. Then add potassium permanganate 10 g. in small portions and heat gently for 5 to 10 minutes, the liquid remaining at least pink. Cool, and add small pieces of ice then sodium bisulphite 15 g. Still keeping the liquid cool, add sulphuric acid 1 : 2, *q.s.*, to acidify. Shake out five times with ether. The residue after distilling off the ether is shaken out with chloroform. This dissolves out the benzoic acid formed. Evaporate and weigh. Multiply resulting weight by 1.468 to obtain quantity of hippuric acid.

INDICAN

Indican, potassium indoxyl sulphate, is excreted in pathologically abnormal quantities in the urine when excessive putrefaction occurs in the intestine.

Indicanuria is most commonly found in intestinal obstruction and severe intestinal inflammations. It may be present in chronic gastritis, gastric cancer and diminished hydrochloric acid secretion. Decomposition of exudates anywhere in the body as in empyema, bronchiectasis and large tuberculous cavities may cause indicanuria.

It is tested for as follows:—To a test-tube one-third full of urine is added an equal quantity of Obermayer's reagent, and a few millilitres of chloroform. OBERMAYER'S REAGENT consists of ferric chloride 2, hydrochloric acid 1000. This makes a yellow fuming liquid which keeps well.) Invert the test-tube a few times to mix. If indican is present in excess the chloroform will assume an indigo blue colour.

Urine of patients taking potassium iodide may give the colour, and this may obscure a strong indican reaction. This can be removed by shaking with a little sodium thiosulphate, leaving the blue of indican. Occasionally, owing to slow oxidation, indigo red will appear instead of indigo blue. This gives a colour much like that due to iodides but it does not disappear when treated with sodium thiosulphate. Bile pigments which interfere with the test must be removed by precipitating with normal lead acetate solution and filtering.

NITROGEN

The total nitrogen of urine varies considerably with the protein intake but the average 24 hours excretion is about 16 g. Of this the urea nitrogen is 14 g., ammonia nitrogen 0.5 g., creatinine nitrogen 1.5 g., uric acid nitrogen 0.25 g. with a little undetermined nitrogen. The fluctuations in amount are nearly always due to variations in the urea excretion which accounts for about 90% of the total nitrogen. Nitrogen is best estimated by some form of Kjeldahl's method. 5 ml. of urine heated in a Kjeldahl flask with 10 ml. of concentrated sulphuric acid, a few crystals of potassium sulphate and 0.5 ml. of saturated copper sulphate solution until all organic matter is destroyed. The solution is diluted with water and after cautious addition of an excess of 40% sodium hydroxide the ammonia formed is distilled into sulphuric acid. The amount of N/5 sulphuric acid neutralised by the ammonia is found by titration with N/10 sodium hydroxide.

Folin and Denis' Method of Estimating Total Nitrogen. Modified Nessler Reagent. Folin and Denis criticise the composition of Nessler's reagent as being excessively alkaline and containing too little potassium iodide. They dissolve potassium iodide 75 g. in warm water 50 ml., add mercuric iodide 0.5 g. and stir. Dilute with water 400 or 500 ml., filter and make up to 1 litre. To 300 ml. of this double iodide solution add 200 ml. of 10% sodium hydroxide, 10 ml. of water and mix. This final solution contains 2% of sodium hydroxide, which is preferable for Nesslerising digestion mixtures of samples of urine.

15 ml. of this reagent added quickly to the digestion mixture will yield *clear* mixtures with as large amounts of ammonia as are met with in the method (0.7 to 1.6 mg. ammonia nitrogen).—O. Folin and W. Denis, *J. biol. Chem.*, 1916, 473. For further data see 18th Edn., Vol. II, p. 422.

The **ammonia nitrogen** rises to relatively high levels in all conditions of acidosis. The usual ratio of ammonia nitrogen to urea nitrogen is 1 to 20. In severe acidosis it may be 1 to 2.

Ammonia nitrogen may be rapidly estimated in urine by the formaldehyde method. 25 ml. of urine to which have been added a few crystals of neutral potassium oxalate are titrated to the neutral point of phenolphthalein with N/10 sodium hydroxide. To this is added 5 ml. of 40% formaldehyde previously neutralised to phenolphthalein. Formaldehyde reacts with neutral ammonium salts liberating an equivalent amount of acid. $4\text{NH}_4\text{Cl} + 6\text{H}\cdot\text{CHO} = \text{N}_4(\text{CH}_2)_6 + 4\text{HCl} + 6\text{H}_2\text{O}$. The acid produced is titrated with N/10 sodium hydroxide. 1 ml. of N/10 sodium hydroxide is equivalent to 0.0014 g. of ammonia nitrogen.

This method also estimates any amino-acids that may be present, but these are negligible except in rare circumstances.

The ammonia in urine may be estimated by distillation and Nesslerisation of the distillate or by aid of volumetric acid, as above.

For Malfatti's method, see 18th Edn., p. 423.

PENTOSE

Bial's Test (P.G. VI). Orcin 1 g. in 500 ml. of concentrated hydrochloric acid containing 25 drops of ferric chloride solution.

Method of Use. To 10 parts of reagent add 1 part of urine and bring just to the boil. Allow to stand until cold. Pentoses yield a green colour and a bluish green precipitate. Glycuronates will give the same reaction only after thorough boiling. After cooling, shake out with 2 parts of amyl alcohol. The amyl alcohol extract will be green, and spectroscopic examination will show a band between the C and D lines overlapping the D line. A second band nearer the red band of the spectrum is not of any significance. A green colour alone is not proof of the presence of a pentose.

Alkaptonuria is due to the presence of dioxyphenyl acetic acid.

Alkapton urine is normal in colour when freshly passed but rapidly darkens on exposure to air and light. The oxidation is hastened by alkali. It reduces Fehling's solution and also solution of silver nitrate in the cold.

Ferric Chloride Test for alkaptonuria. 5% solution of ferric chloride is added drop by drop to 10 ml. of urine in a test-tube. With each drop a fleeting blue colour is given if homogentisic acid be present.

Pentosuria and alkaptonuria are fully described in *Inborn Errors of Metabolism* by Sir A. E. Garrod.

PHOSPHATES

Phosphoric acid exists in urine as salts of sodium, potassium, ammonium, calcium and magnesium. Excretion of phosphates is very variable; the average for 24 hours is 2.5 g. as P_2O_5 . The organic phosphorus content of urine is very small, being about 2% of the total. Estimation of urinary phosphates is of no value except as part of a complete metabolism experiment where intake of phosphorus is known. It is usually estimated by titration with standard uranic acetate, potassium ferrocyanide being used as an external indicator.—*Practical Physiological Chemistry*, Hawk and Bergheim.

Deposition of earthy phosphates in urine is usually due to change of reaction rather than a true increase of excretion. Inorganic phosphate content of blood plasma 2 to 4 mg. per 100 ml.; children, 4 to 5 mg. Decreased in active rickets and by insulin. Increased in chronic nephritis, healing of major fracture, diabetic coma. Estimated by method of Briggs, *J. biol. Chem.*, 1922, 53, 12.

PURINES

Of the known purine bodies, xanthine, hypoxanthine, adenine, guanine, caffeine, theobromine, are met with in food, and uric acid, xanthine, and traces of methylxanthine are found in urine.

They all contain the grouping C_5N_4 —xanthine is dioxypurine, uric acid is trioxypurine. Uric acid is in the largest proportion—about 10 to 1 of the other purines.

There is no special therapeutic effect in a purine-free diet.

Guanidine Metabolism. Its action on administration is to produce symptoms identical with those seen after removal of the parathyroid gland. Correlation needed in terms of metabolic change of arginine with its guanidine nucleus, the guanidine bases themselves and creatine with its methylated group.—*Ann. Rep. chem. Soc.*, 1918, 152.

Suggestion that the guanidine bases are in part or wholly responsible for the cause of the hypertension so often concomitant with nephritis, owing to the fact that guanidine constricts the capillaries.—per *J. Amer. med. Ass.*, ii/1925, 167.

PUS

On finding pus in the urine it should be examined bacteriologically to ascertain the nature of the infecting agent. Radiological examinations may be necessary also to rule out the question of calculus.

In women, a catheter specimen of urine is required, but in men it is possible to obtain a suitable specimen without catheterisation if the glans penis is carefully cleaned and the patient instructed to pass the first portion of urine into an ordinary receiver and the next portion into a sterile wide-mouthed bottle. The specimen must be despatched to the laboratory immediately after collection.

Microscopic examination is essential when pus cells are found in the centrifuged deposit: a count should be made of the number of cells per cubic millimetre. A drop of the fresh uncentrifuged urine is examined in a counting chamber. A few leucocytes may be present in the urine in health, and as the result of several thousand tests C. E. Dukes has shown that 0 to 10 leucocytes may be present per cubic millimetre in the urine of healthy people; he suggests as a definition of pus "more than 100 leucocytes per cubic millimetre." The intermediate zone between 10 and 100 is described as the zone of excess of leucocytes. Degrees of pyuria have been defined by Dukes as follows:—0-1000 pus, 1000-10,000 pus +, and 10,000-100,000 pus + +.

Mucus threads are sometimes found in the urine of male patients who have had gonorrhœa several years previously. These appear as a long thread-like process of mucous uniting chains of pus cells. They are common after prostatic massage and may be present only in the first morning specimen.

Cholesterin is rarely found. It is usually derived from a collection of pus that has been retained in a cavity for some time, ultimately discharging into the urine.

To separate cholesterin, extract the specimen with alcohol-free ether. Purify the residue on evaporation, by dissolving in strong alcoholic potash, evaporating, extracting again with ether, and this again with boiling alcohol—rhombic plates. Chloroformic solution of cholesterin with sulphuric acid gives a red to purple colour. An alcoholic solution so treated gives red to blue.

RENAL FUNCTION TESTS

The tests are of chief value in certain surgical conditions, in the albuminurias of pregnancy and in the diagnosis and prognosis of medical cases of kidney disease. In surgical cases of obstruction of the blood urea has been found to be the most useful test of kidney function. A blood urea content above 60 mg. per 100 ml. contradicts prostatectomy in one stage. In other types of surgical cases the dye excretion tests are most satisfactory and are usually performed by the surgeon himself.

In cases of albuminuria in pregnancy with clinical symptoms such as headache, vomiting and œdema, as in nephritis toxæmia (see Wesselow) there is marked nitrogen retention, with a blood urea above 40 mg. per 100 ml. and a high blood pressure. In threatened eclampsia there is albuminuria, diminished urea output and frequently an increased blood urea, but the imminence of eclampsia cannot be judged from the amount of nitrogen retention.

In medical cases of kidney disease, renal function tests are often useful but it must be borne in mind that obstruction to urinary

outflow produces much greater nitrogen retention than severe kidney disease. Blood analysis is particularly useful in checking the effects of diet in cases of nephritis with nitrogen retention. Similarly in parenchymatous nephritis the value of treatment can be assessed by the reduction in blood cholesterol. Whatever tests are performed their value must always be weighed in the light of information gained from general clinical examination, the blood pressure and condition of the arteries.

Of the numerous tests devised for estimating the functional activity of the kidneys the following have proved the most reliable in practice.

(1) **Systematic examination of the urine** (including the record of the total quantity passed each day, the specific gravity, the presence of albumin, blood, and pus, and the presence of casts). If the patient is on a standard diet and accurate daily quantitative tests can be made, useful information can be obtained from quantitative tests of urinary constituents, particularly of the urea and chlorides in the urine, but this method has only a limited applicability in practice. The following table (from *Recent Advances in Medicine*, by Beaumont and Dodd, 4th Edn., p. 23), gives figures obtained at the Middlesex Hospital.

Table showing analyses of twenty-four hours' urine of typical cases of renal inefficiency.

Case.	Vol. ml.	Albu- min per 1000	Urea g.	Uric Acid g.	Creati- nine g.	Total N. g.	Chlor- ides g.
Normal men . .	1500	—	30	0·6 to 1·2	1 to 1·25	14 to 16	10 to 15
Acute nephritis	300	20	7	0·2	0·8	6	1·7
Chronic intersti- tial nephritis	3000	0·5	15	0·6	0·9	8	14·8
Large white kidney . .	1000	10	14	0·72	0·85	7	1·7
Small white kidney . .	1800	12	12	0·84	0·79	6·4	0·9

(2) **Blood Tests.** *Blood Urea Estimation* is of chief value in suspected cases of nitrogen retention, particularly in the diagnosis of uræmia and urinary obstruction.

The urea in the urine (see *Urea*) should be estimated at the same time. In marked cases of uræmia the blood urea is often (but not invariably) above 100 mg. In interpreting figures between 50 and 100 mg. the limitations of the test must be kept in mind, namely, the fact that any disease, such as diarrhoea or diabetes, which leads to severe anhydræmia tends to raise blood urea. Similar effects are produced by a failing circulation.

due to a fall in blood pressure. Therefore it is often difficult to assess the value of the test in patients who are very ill. In general, it may be said that marked nitrogen retention and therefore high blood urea occurs in chronic interstitial nephritis and with urinary obstruction. Little or no retention is found in parenchymatous nephritis until the terminal stages.

A blood urea content as high as 300 or even, in rare instances, of 400 mg. per 100 ml. is not incompatible with recovery in an acute case of nephritis, and even in chronic types, in which the capacity is of necessity less, a blood urea content of 100 to 200 mg. does not necessarily imply a speedy death. Inorganic phosphate estimation of value. Phosphorus is more definitely connected with symptoms of true uræmia than is the retention of urea.—O. L. V. de Wesselow, *Lancet*, i/1923, 163.

Blood urea may be most conveniently estimated by the micro-method described by Archer (*Quart. J. Med.*, 1925, 274). Most modern methods for estimation of urea in blood depend upon the use of the ferment urease from soya bean to convert the urea into ammonium carbonate. The ammonia thus produced is estimated either colorimetrically by Nesslerisation or volumetrically after distillation. Good descriptions of various renal efficiency tests are given in Harrison's *Chemical Methods in Clinical Medicine*. For medical cases Van Slyke's Urea Clearance Test (*q.v.*) is simple and useful but of no value where there is residual urine in the bladder or where collection cannot be accurately controlled.

Chemical Spot Test in Diagnosis of Uræmia. To Ehrlich's aldehyde reagent add 20% trichloroacetic acid with shaking until the cloudiness forming with each drop just faintly persists.

Technique. To a small volume of blood in a narrow test-tube add an approximate volume of the reagent. Shake vigorously for a few seconds and then pour a drop of the coagulum on to a white filter paper. The filtrate spreads in an extending circle leaving a brown centre of precipitated protein. With true uræmia, the spot external to this dark centre is a distinct green colour; when dry, the yellow colour of this spot slowly intensifies, becoming a bright canary yellow after several hours, while bloods with only a little or no urea retention leave only a dull pale green spot. Not a substitute for blood-urea estimation but suitable for emergencies to ascertain whether or not there is gross retention of nitrogen.—J. Patterson, *Lancet*, i/1934, 1061.

Andrewes' simplified Diazo Test for Uræmia is carried out by removing the proteins from the serum by adding 2 vols. of absolute alcohol and centrifuging or filtering. To 4 vols. of the filtrate is added 1 vol. of diazo reagent—this is the same as that used in Van den Bergh's Test, *q.v.*—and the mixture boiled for $\frac{1}{2}$ to 1 minute when 40% soda solution is added drop by drop, shaking after each dilution. The test is positive only when a deep pink or cherry red colour is seen, which colour may last only for a few seconds.—G. A. Harrison and L. F. Hewitt, *Brit. med. J.*, ii/1927, 1138. (This reaction is due to a high concentration of indican in the blood.)

(3) **Elimination Tests.** The **Urea Concentration Test** is the most popular. The principle is to give a large dose of urea (15 g.) *per os* and observe how rapidly the kidney removes the excess. The test is best carried out first thing in the morning.

Technique. The patient is allowed no food or drink after 10 p.m. the previous night. At 5.58 a.m. the bladder is emptied completely and this specimen of urine marked "0." At 6 a.m. he takes the following mixture, urea 15 g., tincture of orange 10 ml. and water 100 ml. At 7 a.m. he empties his bladder completely, this specimen being marked "1." At 8 and 9 a.m. he passes urine again, these specimens being marked "2" and "3" respectively. The total quantity of urine passed at 7, 8 and 9 a.m. must be measured. This should not exceed 120 ml. in No. "1"

and 100 ml. in Nos. "2" and "3." If more than this is passed it indicates that the urea has a diuretic action and a low urea concentration may not necessarily mean a poor renal function.

Normally the concentration of urea in one or other specimen is at least 2·5% or 3%. In renal inadequacy it is below 2%.

The chief limitations of the test are that in the hydræmic type of nephritis with chloride retention it may give normal results even when the patient is very ill, because in this disease there is not necessarily any nitrogen retention. In cases of enlarged prostate with residual urine the first two specimens may be influenced by dilution with this residue but by the third hour the real concentration should be apparent. Sometimes it is useful to collect a specimen at 4 hours.

Phenolsulphonaphthalein (Phenol red) Test. An aid in proving whether the diminished excretion of nitrogen is due to interference with function and also a guide to the degree of interference with renal function in toxæmia of pregnancy and threatened eclampsia.

Give 300 to 400 ml. of water half an hour prior to the test. Empty the bladder with a catheter and give intramuscularly, or preferably intravenously, in the upper arm 6 mg. of phenolsulphonaphthalein neutralised with sodium hydroxide in 1 ml. of water ("Sterules" of this strength are made).

The urine is collected in test-tubes containing a few drops of potassium hydroxide solution. Normally the red colour appears in 5 to 10 minutes, is at its maximum in 15 to 20 minutes, and all the dye is excreted in 4 hours. There is reason to suspect deranged function when any of these times is increased.

Rowntree and Geraghty think that investigations on the lines of urea output, total nitrogen value, etc., are of no value.

In severe acute nephritis the permeability is markedly decreased, also in chronic interstitial nephritis. The delayed appearance and especially the diminished excretion in the 2-hour period are more accurate indications of functional derangement than an estimation of total solids or nitrogen.

The removal of blood and bile from the urine for the test by precipitation of hæmoglobin and bilirubin on addition of equal volume of saturated alcohol and zinc acetate.—*J. Amer. med. Ass.*, ii/1925, 1749.

In the stools of 9 out of 26 patients, after intravenous injection of 6 mg. 1% to 8% of the amount injected was recovered, showing that the dye may be eliminated, re-absorbed, and transformed in the digestive tract. The duodenal tube, immediately after the injection, showed presence of 1% to 3% of the dye in the bile of three normals, while it was absent in the bile of five persons with liver disease.—*J. Amer. med. Ass.*, ii/1925, 309.

By tests on normals in which the urine was collected at 15-minute intervals for 2 hours, the curve of dye elimination by the kidneys was shown to be 40% during the first 15-minute period, 17% during the second, 8% during the third, and 4% during the fourth, gradually decreasing to 0·5% during the eighth. A series of cases of known renal insufficiency showed abnormality in the curve, the presence of an abnormal curve indicating impending renal failure, while the other tests were negative.—*J. Amer. med. Ass.*, ii/1925, 46.

In normal kidneys the colour appears in 5 to 10 minutes and the maximum colour in 15 to 20 minutes, while the total excretion should be complete in 4 hours.—G. A. Harrison, *Lancet*, ii/1928, 1144.

Very favourably impressed with this test. Widely used in American urological practice.—K. Watkins, *Brit. med. J.*, i/1934, 209.

Indigo Carmine Test. Indigo carmine "Sterules" (Intravenous) contain 10 ml. of a saturated solution (approx. 1%). "Sterules" are also made containing 10 ml. of 0·4%. For testing kidney permeability. Confusion has arisen as to the strengths of these solutions. They are given undiluted.

Solutions stronger than 0·4% should not be used at all. The substance should not contain more than 1% of salt, and should be tested according to the Fr. C. and the new B.P. methods, and physiologically.

Cystoscopic examination of the urethral openings and the urine gives, by depth of colour, indication of renal functional power.

The cystoscope should be introduced immediately after the injection and the urethric orifices carefully watched, when the ejection should appear as a forcible dark blue jet. Parenchymatous or interstitial nephritis is suggested by delay in excretion from both ureters. Marked delay on one side indicates disease: thus, if 8 to 12 minutes after injection, suggests chronic pyelitis. If 2 to 18 minutes elapse before elimination, partial urethral obstruction or moderate impairment of renal function is indicated. 20 minutes' delay indicates almost complete obstruction, or serious disease of the kidney or ureter.—*Urinary Analysis*, L. Heitzmann. See also Choyce's *Surgery*.

Intramuscular injections (10 ml. of 0.4%) have also been used. Here also confusion has existed concerning the strength employed. The colour should appear in the urine in 10 to 12 minutes if functional capacity is in order.

Best results obtained by giving a small quantity, 5 ml. of 0.4% solution intravenously, the excretion of the dye beginning 4 to 5 minutes afterwards. If a larger quantity be injected the blue coloration is so intense that the cystoscopic medium becomes obscured and it may be impossible to discover any difference in the colour from the two ureters. A good elimination of the dye does not preclude a minute tuberculous lesion of the kidney.—J. Swift Joly, *Brit. med. J.*, ii/1927, 847. See also H. Maclean, *Brit. med. J.*, ii/1921, 426.

Collapse following intravenous injection of 2 ml. of 4% solution—actually a suspension. No concentration more than 0.4% should be used intravenously.—A. E. Roche, *Brit. med. J.*, i/1928, 921; ii/1928, 778.

In normal kidneys the colour appears within 5 to 20 minutes, the maximum colour should appear in 45 minutes, and total excretion should be complete in 4 hours.—G. A. Harrison, *Lancet*, ii/1928, 1144.

Tests of renal efficiency.—G. A. Harrison, *Lancet*, ii/1928, 1092.

Methylene Blue Test. 1 ml. of 1 in 20 solution is injected into the gluteus maximus and the urine is turned pale green in half an hour, the colour increasing up to the fourth hour. "Sterules" of this strength are prepared.

The method is sufficient to compare the work of the two kidneys, but the indigo carmine method is better.

Phloridzin Test. This consists in injecting 5 to 10 mg. of phloridzin (see also Vol. I, p. 873, and this Vol.) subcutaneously in 20 to 30 minims of water. Glucose should normally appear in the urine in half an hour.

This test is also delicate for determining which kidney is diseased.

The technique of Caspar's method consists in the subcutaneous injection into the buttock of 1 ml. of 1% phloridzin solution and observation as to (a) excretion of sugar by a healthy kidney or (b) non-excretion or more slowly and to less extent (diseased).

Creatinine has been found an excellent substance as a test for renal function. As a result of experiments it was concluded that in normal persons and those with no real lesions the intravenous injection of 0.5 g. of creatinine is followed by increased excretion. In chronic nephritis the increase is either *nil* or under 50%. It should serve as a useful confirmation of other methods.—R. H. Major, *Per Prescriber*, 1923, 160.

The following is critical: Phenolsulphonaphthalein test of no prognostic value. Urea concentration test—results misleading, unless taken in conjunction with urea content of blood. Urea content of blood no guide to prognosis, nor commensurate with severity of symptoms. In general, the tests do not give any more definite evidence of severity of disease, or of probable outcome. They do not give any help in distinguishing between acute, sub-acute and chronic cases, and during disease merely corroborate clinical symptoms.—E. Crawford, *Lancet*, ii/1924, 78.

Special Committee on Renal Function. Urea concentration test, standard method. Blood urea test, diastase test, phenol dye and indigo carmine tests.—*Lancet*, ii/1922, 71.

Van Slyke's Blood Urea Clearance Test.

Definition of Augmentation Limit. When the urinary volume is relatively large the amount of urea excreted per minute is directly proportional to the blood urea content. When the urinary volume is small this relation no longer holds. Van Slyke *et al.* called the urinary volume above which this relation does hold the "*augmentation limit*" (augmentation of urinary volume beyond this limit does not increase the rate of urea excretion). The usual

augmentation limit in adults is about 2 ml. of urine per minute. When the urinary volume is 2 ml. or more per minute, calculate the maximum blood urea clearance. When the urinary volume is below 2 ml. per minute, calculate the standard clearance.

Maximum Blood Urea Clearance. Above the augmentation limit increase of urinary volume does not increase the amount of urea excreted in urine per minute; i.e., the average amount of urea excreted per minute remains constant. Therefore, on the basis of the idea that the blood is *completely* cleared of urea as it passes through the kidneys (which, of course, it is not), the number of millilitres of blood cleared of urea per minute remains constant. Let the maximum clearance be denoted by C_m .

Suppose the volume of urine excreted per minute = V ml.,
and the concentration of urea in this urine = U mg. per ml.
Therefore, urea excreted in urine per minute = $U \times V$ mg. Since $U \times V$ mg. of urea are excreted in urine per minute, therefore the same amount ($U \times V$ mg.) must be removed from the blood in one minute. Suppose the blood contains B mg. of urea per 1 ml.

Therefore 1 mg. of urea is contained in $\frac{1}{B}$ ml. of blood,

therefore $U \times V$ mg. of urea is contained in $\frac{U \times V}{B}$ ml. of blood,

i.e., $\frac{U \times V}{B}$ ml. of blood are completely cleared of urea per minute,

$$\text{or } C_m = \frac{U \times V}{B} \text{ ml. of blood per minute.}$$

Provided that U and B are expressed in the same terms, it does not matter whether mg. per 1 ml. or mg. per 100 ml. or g. per cent. or g. per litre is used. The urinary volume V , however, must be expressed in millilitres of urine per minute.

Example.

$$V = 150 \text{ ml. per hour} = 2.5 \text{ ml. per minute.}$$

$$U = 1\% = 1000 \text{ mg./100 ml.} = 10 \text{ mg. per 1 ml.}$$

$$B = 50 \text{ mg./100 ml.} = 0.5 \text{ mg. per 1 ml.}$$

$$C_m = \frac{UV}{B} = \frac{10 \times 2.5}{0.5} = 50 \text{ ml. of blood per minute}$$

or since average normal = 75 ml. of blood per minute,

$$\text{therefore } C_m = \frac{50}{75} \times 100 = 67\% \text{ of average normal.}$$

Standard Blood Urea Clearance. Below the augmentation limit, the number of millilitres of blood cleared of urea per minute is not constant, but varies, on the average, with the square root of the urinary volume. It is, therefore, necessary to fix the urinary volume at a definite standard (which is not practicable), or to calculate by means of the square root rule from the observed urea excretion what would be the urea excretion which would accompany such a standard urine volume.

Suppose C is the observed blood urea clearance when the urinary volume is V ml. per minute. Let C_s be the *standard* blood urea clearance with a corresponding *standard* urinary volume of V_s ml. per minute.

$$\text{Then } C_s : C :: \sqrt{V_s} : \sqrt{V}$$

$$\text{or } C_s = \frac{C \sqrt{V_s}}{\sqrt{V}}$$

As *standard* urinary volume (V_s), Van Slyke *et al.* adopt 1 ml. per minute (= 1440 ml. per 24 hours)

$$\text{Therefore } C_s = \frac{C \times 1}{\sqrt{V}}$$

But C , the observed clearance, as we have seen for C_m , the maximum clearance, is equal to $\frac{U \times V}{B}$.

substituting for C

$$Cs = \frac{U \times V}{B} \times \frac{1}{\sqrt{V}}$$

$$\text{i.e., } Cs = \frac{U \times \sqrt{V}}{B} \text{ ml. of blood per minute.}$$

In health the average values of Cm and Cs have been found to be 75 ml. and 4 ml. respectively.

Results can, therefore, be expressed as percentages of average normal, instead of as so many millilitres of blood per minute. Thus comparisons can be made between Cm of one patient and Cs of another patient.—*J. clin. Invest.*, 1928, 3, 47; *Quantitative Clinical Chemistry*, Peters and Van Slyke, Vol. I, p. 345, and Vol. II, pp. 564, 935.

A defect in renal function might be revealed by this test when blood urea was still within normal limits. The influence of a minor surgical operation on renal function showed that on the day following operation the urea clearance value fell from 76% to 52% but returned to original level next day. Really nothing to worry about until figure shown by the test was 40% or less.—C. Dukes, *Brit. med. J.*, i/1934, 209.

From a surgical point of view the most valuable test available, especially in prostatic cases where a figure of 60% might be taken as the border line to indicate whether a one-stage or two-stage operation should be performed.—E. W. Riches, *ibid*, 209.

UREA

Average content in the urine is 2.5% to 3%, or about (in health) 500 grains (33 g.) per diem; it may range between 15 g. and 40 g. The majority of methods are based on the decomposition of urea into nitrogen, carbon dioxide, and water when treated with sodium hypobromite. The carbon dioxide is absorbed by the excess of alkali present, and the nitrogen can be measured, from which, on reference to tables, the percentage can be found—theoretically 1 ml. of nitrogen at 0° = 0.0027 g. approximately of urea. In the process about 8% of the total nitrogen is suppressed, but the increase in volume of the gas due to the room temperature (taken as 18°) and the vapour tension (the gas being measured moist) has been found in practice to compensate almost exactly for this loss.

The average urea content in urine was found to be 1.6% in the case of patients under observation in hospital. When the kidneys are damaged the concentration falls below that figure. That the specific gravity of the urine is consistently low in advanced granular kidney disease is a well recognised fact. Salt retention is a characteristic of the oedematous or tubal type of nephritis just as urea retention is characteristic of the chronic interstitial or cirrhotic type.—C. R. Box, *Brit. med. J.*, i/1920, 356.

Sodium Hypobromite Solution, *syn.* PAYNE'S REAGENT. Sodium hydroxide 100 g.; distilled water 250 ml. Dissolve, cool, and keep iced while adding *guttatim* bromine 25 ml. Mix and dissolve. This solution is used to estimate the amount of urea in a given quantity of urine. On adding the solution, nitrogen is evolved from the urea and is measured in a Doremus ureometer.

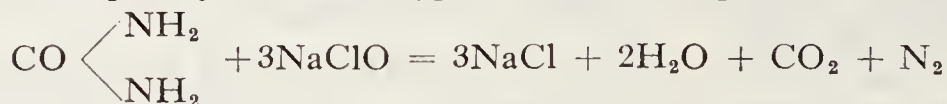
It is better to keep the bromine separate; it may be used in "Sterules" containing 2, 3 and 4 ml. respectively; 1 ml. of bromine should be added to 11 ml. of the solution as required. In place of these,

Liquor Bromi (bromine 1 ml., potassium bromide 1.5 g., distilled water 10 ml. to 11 ml.) may be used in equal quantity to the soda solution.

Apparatus. 100 ml. graduated tube connected at the lower end by rubber tubing with a levelling tube, and at the upper end with a small bottle. The

bottle is closed by a rubber cork having two holes with glass tubing through the holes, one being connected by rubber tubing to the upper end of the graduated tube, the other closed by a short piece of rubber tubing and screw clip. The bottle contains a small test-tube which will just lie obliquely. Put 25 ml. of hypobromite solution in the bottle and 4 ml. of urine into the test-tube. Insert cork and, with screw clip open, adjust the levelling tube until water in the graduated tube is at the 0 mark; close clip. Tilt bottle until all the contents of the test-tube are spilled into the hypobromite. When the reaction has finished, adjust levels and read off number of millilitres of gas evolved. Each millilitre of nitrogen $\times 0.0625 =$ the percentage of urea present. For full details see *Chemical Methods in Clinical Medicine*, Harrison.

Sodium hypobromite has been found more accurate than sodium hypochlorite which was at one time used for the purpose—the nitrogen being evolved more rapidly and completely. Sodium hypochlorite decomposes urea as follows:—



With hypobromite the reaction is analogous.

The chief cause of low results in the hypobromite method appears to be the presence of undecomposed urea, this difficulty being obviated by carrying out the reaction in warm solution.—*J. chem. Soc. Abstr.*, ii/1924, 591.

A further explanation which has been given for the decomposition of only 90% of the urea present (using hypobromite) is that sodium cyanate is formed.—M. D. Donald, *Chem. & Drugg.*, ii/1925, 894.

Xanthydrol has been applied to the quantitative determination of urea in urine with which it forms dixanthylurea, $[\text{O}(\text{C}_6\text{H}_4)_2\text{CH}\cdot\text{NH}]_2\text{CO}$. Other constituents of urine do not interfere.

To 5 ml. of urine add 3.5 ml. of glacial acetic acid and 1 ml. of 10% solution of the reagent in methyl alcohol, followed by four further additions of 1 ml. at 10-minute intervals. After one hour, collect the precipitate on a sintered glass filter, wash twice with acetic acid (66%), then with alcohol and finally remove alcohol with water. Grind the precipitate with small portions of a cold mixture of equal volumes of N/1 potassium dichromate and concentrated sulphuric acid, the volume of the mixture being gradually increased until 50 ml. in all has been added; then boil for 5 minutes. Cool, dilute to 250 ml., and titrate the excess dichromate in an aliquot portion by means of iodide and sodium thiosulphate. One molecule of dixanthylurea requires 58 atoms of oxygen, and 1 ml. of N/1 potassium dichromate is equivalent to 0.517 mg. of urea.—per A. D. Mitchell, Lecture to Institute of Chemistry, Oct. 19, 1934.

Urease Method of Estimating Urea. Mix 25 ml. of the urine with a pinch of powdered soya bean flour (2 to 3 g.). Allow to stand overnight covered with a small layer of xylol or benzene. Render the liquid alkaline with strong sodium carbonate solution and distil into standard hydrochloric or sulphuric acid by Kjeldahl's procedure. Urease only attacks urea, 1 molecule of urea producing 1 molecule of ammonium carbonate $(\text{NH}_4)_2\text{CO}_3$, and there may be present a small amount of ammonium salts in addition to free ammonia. For accurate work these must be estimated separately.

Urease Preparation. Cover 200 g. of finely powdered soya bean with 1000 ml. of water and keep 6 hours. Treat the filtrate with 96% alcohol (400 ml.) as long as precipitate forms. Collect and dry slowly and add lactose *q.s.* to 100 g. Keep the product dry.—*Biochem. Z.*, 1922, 134, 336, per *Yearb. Pharm.*, 1923, 154; *C.R. Soc. Biol.*, Paris, 1924, 50, 6017, per *Yearb. Pharm.*, 1924, 142.

Urea Nitrogen Determination by Direct Nesslerisation. Urease is used as above for hydrolysis of the urea, either in the form of the enzyme or as soya bean meal. It decomposes urea quantitatively and does not affect other constituents of urine.

Place 1 ml. of the urine in a 100 ml. graduated flask. Add 0.1 to 0.25 g. of soya bean meal in the form of a 1% suspension. Allow to stand for one hour at room temperature, or 15 minutes at about 50°. Add 25 ml. of water and 1 ml. of *m*-phosphoric acid solution (25%) and mix, then add 1 g. of pure blood charcoal, shake, make up to volume, mix, and filter.

(The soya bean meal suspension is made thus: Rub 5 g. with water 15 ml. to a smooth paste. Add more water *q.s.* to about 400 ml. Add 100 ml. of alcohol 10 to 15 ml. of this are used. It keeps good for about 2 days.)

Place 5 to 20 ml. of the filtrate in a 100 ml. graduated flask. (The amount taken should contain 0.7 to 1.3 mg. of ammonia nitrogen.) Dilute to 60 or 70 ml. nesslerise with the modified Nessler reagent, *v. p.* 325 and compare with standard 1 mg. of ammonia nesslerised in another 100 ml. flask).

The determination of minute quantities of urea by hydrolysis with acid at 50° followed by nesslerisation.—J. T. Wearn and A. N. Richards, *J. biol. chem.*, 1925, 66, 275.

URIC ACID

The average content in the urine is 0.05% to 0.06%. This is derived from endogenous and exogenous sources. The exogenous uric acid fluctuates with the amount of nucleoprotein in the diet. Estimations of uric acid in the urine are only of value where diet is known and uric acid excretion over a period is being estimated. In gout there is a deficient excretion of uric acid.

Pratt and Barker (*Endocrinology and Metabolism*) found that endogenous excretion in 20 gouty patients was 250 g. per diem compared with 390 mg. in 20 normal patients.

When pure, uric acid occurs as white crystals, very slightly soluble in water, insoluble in alcohol and ether.

Heated to dryness on a water-bath with a little nitric acid or potassium chlorate and hydrochloric acid in a white dish, cooled, and a little ammonia solution added, gives a red colour—the **Murexide Reaction**.

DETERMINATION

Hopkins' Method.—To 100 ml. of sample add about 30 g. of ammonium chloride in powder, dissolve as completely as possible, or a small quantity may remain undissolved, add a little ammonia to neutralise and allow to stand for 10 minutes. Filter off the precipitated acid ammonium urate, wash with saturated ammonium sulphate solution and rinse off the precipitate from the filter with water to 100 ml. Add 20 ml. concentrated sulphuric acid to raise temperature of the liquid to about 60°, or, if necessary, warm to that temperature. Titrate with N/20 potassium permanganate (1.58 g. in 1 litre), taking as end-reaction the point at which the permanganate ceases to be instantly decolorised. Each ml. of the permanganate solution = 0.00375 g. uric acid.

Gowland-Hopkins' Method is the same as the above until the acid ammonium urate has been washed with ammonium sulphate solution, then proceed as follows:—Wash off the precipitate into a small beaker with a jet of hot water, add a little hydrochloric acid, and heat just to boiling. Allow to stand two hours in the cold. Collect the separated uric acid, measuring the filtrate at the same time, for which an allowance of 1 mg. must be added on to the final result for every 15 ml.; it need not exceed 20 to 30 ml. Wash the uric acid crystals with a little distilled water, rinse off the filter with hot water, warm with sodium carbonate till dissolved and make up with water to 100 ml. Add 20 ml. of sulphuric acid and titrate with permanganate as above, adding it slowly towards the end of the reaction, the finish being the first appearance of a pink colour which is permanent for an appreciable interval. Previously the disappearance of the colour is instantaneous.

Phosphotungstic Acid Test. (A rapid approximation.) Mix about 10 ml. of urine with 3 ml. of solution of potash, add 20 drops of a 20% solution of phosphotungstic acid. Uric acid causes a blue colour which varies in depth with the proportion present. The method is not applicable for anything approaching an accurate colorimetric estimation since the colour fades rapidly. Use a standard for comparison of 1 in 50,000 uric acid.

The test can also be conducted by heating the urine with solution of potash and a 5% solution of phosphotungstic acid, which gives a lilac colour. The intensity can be compared with that given by a standard solution of uric acid in 1000.

The following **modification of Folin's method** for the colorimetric determination of uric acid avoids difficulties due to the turbidity of the final solutions:—1 ml. or more of urine is mixed with 3 ml. of water and 3 ml. Folin's acid silver lactate solution, allowed to stand in the dark for a few minutes, and centrifuged. The precipitate is dissolved in 5 ml. of Folin's cyanide and urea reagent (see below), and the solution transferred quantitatively to a 100 ml. flask by means of 2 portions of 10 ml. each of 10% sodium carbonate solution and 5 ml. of water. 5 ml. of uric acid reagent is added, the contents mixed and then after 5 minutes diluted to 100 mls., and the colour compared with a standard prepared by diluting to 100 ml. 5 ml. of standard uric acid solution containing 0.1 mg. of uric acid per ml., 5 ml. of cyanide and urea reagent, 20 ml. of 10% sodium carbonate solution, and 5 ml. of the uric acid reagent.—H. B. Salt *Biochem. J.*, 1931, 1720.

The acid silver lactate solution is prepared by dissolving 100 g. of silver lactate in 700 ml. of water containing 100 ml. of lactic acid (85%) partly neutralised by 100 ml. of 10% sodium hydroxide.—O. Folin, *J. biol. Chem.*, 1922, 54, 153.

Cyanide-Urea Reagent. Add 50 g. of sodium cyanide to 700 ml. of water and stir until dissolved. Add 300 g. of pure urea and stir until practically complete solution is obtained. Transfer to a 2 litre flask, add 5 to 6 g. of pure calcium oxide and shake for 5 minutes. Filter and store in tightly stoppered bottles.—O. Folin, *J. biol. Chem.*, 1930, 86, 179.

BLOOD

Blood Corpuscles.—The red blood corpuscle has an average diameter of $7.5\mu = \frac{1}{33.86}$ inch. It is discoid in shape with indentations in the two sides. Occasionally it is smaller, e.g., $6\mu (= \frac{1}{42.00}$ inch). Price-Jones determined the diameter in normal human blood to be 6μ to 8.75μ —with an average of 7.4μ , whilst in pernicious anæmia the diameter varied from 4μ to 11.75μ , and the average diameter of five successive 100 cells was 8.0μ .

In disease it may reach 8 to $10\mu = \frac{1}{31.75}$ to $\frac{1}{25.40}$ inch, i.e., anisocytosis, or irregularity in size; further, in disease, the corpuscles may exhibit poikilocytosis, i.e., irregularity in shape. In examination of films, vacuolation should be noticed, as also irregularity in staining (polychromatophilia). With regard to abnormal red cells—these are mainly of two kinds, (1) those like normal cells without nuclei, (2) nucleated. The group (1), where they have special designations, have names ending in *cyte* (*microcyte*, *megalocyte*, etc., based on the type of the normal corpuscle which is called an *erythrocyte*), whilst the nucleated forms have names ending in *blast*. In this group are *normoblasts* and *megaloblasts*.

For details of *white corpuscles* v. p. 342.

Precipitin Test for Blood. Precipitins are formed when the serum of one kind of animal is introduced into the body of another species, e.g., the serum of a horse injected into a goat causes the serum of the goat to be capable of forming a precipitate with normal horse serum.

In using the test for forensic purposes a rabbit is injected with human blood serum. The serum of the rabbit, "**anti-human serum**," when dropped into a clear solution of human serum causes a precipitate—not with the serum from another animal. The principal difficulty in the test is to obtain from the rabbit an anti-human precipitating serum of the proper strength. To be thoroughly reliable and specific *the formation of the precipitate must begin in five minutes and be complete in thirty minutes*. Old blood-stains respond as well as recent

A human blood-stain taken up with normal saline and some anti-human serum added gives a white cloudy ring—not so the stains from animal blood. Specific sera injected into a rabbit form an equally specific anti-serum—in other words, human anti-serum will infallibly detect human blood; a horse anti-serum will detect horse's blood, and so on.—*Pharm. J.*, i/1911, 202.

Indian experience with the test was that it is absolutely trustworthy—the reaction is not effected by the decomposition of the blood, by heat, etc. Fowl's blood used instead of rabbit's. Failures with goat's and monkey's blood.—*Brit. med. J.*, i/1911, 1481.

Recent description of the technique of the precipitin test.—*Analyst*, 1928, 5.

Hydatid Fluid may be used to give precipitin test as aid in diagnosis. Interaction between hydatid fluid and serum from hydatid patients has been obtained.

Hydatid disease. Complement-fixation as mode of diagnosis. Found to be of considerable value in the few cases available—positive results are conclusive, negative difficult to interpret. Hitherto the method of diagnosis has been the verification of eosinophilia—this is, however, characteristic of almost every form of vermiform parasite.—*Lancet*, ii/1910, 377.

Hydatid Skin Test. Intradermal injection of hydatid fluid preserved with 5% phenol a very satisfactory method of diagnosis. About 0.1 ml. injected. Positive result shown by formation of a wheal and a spreading erythema. Eosinophilia is very often absent in hydatid disease.

Blood in urine may be present in gross amount, when the urine is red, or in small quantity, when it is characteristically "smoky." Mere traces of blood are not discernible by the naked eye. The most sensitive test for blood in urine is the microscopical examination of the centrifuged deposit for the presence of red cells. Hæmoglobinuria, such as occurs in paroxysmal hæmoglobinuria, where only the hæmoglobin and not the red cells is present, will not of course be detected by this test.

Spectroscopic examination of urine will show characteristic absorption bands of oxyhæmoglobin unless the specimen is old or decomposing when some may have become methæmoglobin also having a characteristic spectrum. Chemical tests for blood all depend upon the hæmoglobin, in conjunction with some oxidising agent, bringing about the production of some coloured oxidation product. The most useful of these chemical tests is the **Amidopyrine (pyrimidon) Test** carried out as follows: To about 5 ml. of urine add 2 drops of acetic acid (33%). On the surface of this mixture in a test-tube carefully layer about 1 ml. of 5% amidopyrine in alcohol. Drop in 5 to 6 drops of 10 vol. hydrogen peroxide. The presence of blood will be shown by the development of a mauve ring at the junction of the two liquids. Iodides in the urine give a false positive and their presence must be excluded.

Benzidine Test for Blood in Urine and Pathological Material. **Benzidine**, *syn.* *p*-diaminodiphenyl. $\text{NH}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{C}_6\text{H}_4 \cdot \text{NH}_2$. Grey crystalline powder, soluble 1 in 19 of 90% alcohol, insoluble in cold water.

(Benzidine hydrochloride is insoluble in 90% alcohol and in water.)

Employ a 1% solution of the base in 90% alcohol or 1% solution in a mixture of equal parts of glacial acetic acid and water. Whichever is used the result is practically identical. There is merely a difference in the shade of blue produced in the presence of blood.

To apply the test add to 2 ml. of the benzidine solution about the same quantity of 20 volume hydrogen peroxide. Mix and add 2 ml. of the liquid to be tested. A blue colour forms at once if blood is present. The density of the colour corresponds to the amount of blood. Always conduct a control with normal material alongside.

Alternatively, mix 2 ml. of the specimen with a few drops of benzidine solution and layer carefully with ozonic ether. In this case a blue ring is formed. By the above test 1 of blood in 1000 of liquid is easily detected. Indeed, far smaller amounts, even 1 in 100,000, are stated to have been detected.

Diastases, zymases and fruit juices give a similar reaction. A positive reaction does not prove the presence of blood, but a negative proves its absence.

The test is less specific if material has been strongly heated.—*Brit. chem. abstr.*, 1928, 1046.

Tablets of benzidine 0.1 g. and sodium perborate 0.1 g. Just before use, dissolve a tablet in 10 ml. of glacial acetic acid. If a suspected spot on an

article of clothing, etc., is to be examined, it is moistened with a drop of normal saline and well rubbed with a glass rod. The drop is then absorbed in a small piece of absorbent cotton wool and the spot at once treated with a few drops of the reagent. In presence of blood a blue colour is seen. The benzidine test is very sensitive and simple.

Weber's Guaiacum Test. Make an ether extract as above and add 8 to 10 drops of guaiacum tincture and hydrogen peroxide. Definite blue colour in 2 minutes. For albumin add equal volume of saturated solution of ammonium sulphate, filter, acidify and warm.—R. Coope, *Lancet*, ii/1920, 291.

Ozonic Ether and Guaiacum Test. Add a drop or two of tincture of guaiacum—guaiacum resin 1 in alcohol (90%) *q.s.* to 10—to a small quantity of the urine, shake and “layer” ozonic ether on to the mixture. A blue colour at once, or on standing, indicates presence of blood—iodine in the urine also gives this colour (e.g., if patient has been treated with iodides). Further, put gives it with guaiacum tincture alone, the colour disappearing on heating.

Modified Guaiacum Test using Sodium Perborate.—To about 5 ml. of the liquid add 1 to 5 drops of fresh saturated alcoholic solution of guaiacum resin, then about 1 g. of sodium perborate and about 10 ml. of 30% acetic acid. Shake the mixture once and pour alcohol carefully into the tube to form a separate layer,—a blue or blue-green colour at the junction in 5 minutes will be formed, or green if only a trace. The guaiacum resin used must show a brown, not a greenish fractured surface.

This test is said to indicate 0.02 g. of blood per litre, i.e., 1 in 50,000. It is about five times as delicate as the Ozonic Ether Test. A green colour should be disregarded since a blank test gives a green. Fresh solution of guaiacum is stated to have no advantage over seven months' old simple tincture of guaiacum.

Blood Stains on Clothing, etc.—Plunge the cloth into boiling water for a few minutes, place on slide and add a few drops of ammonium sulphide. Examine microspectroscopically for absorption bands of hæmochromogen. May be increased by 10% potassium cyanide solution. If on a weapon or piece of jewellery, moisten with ammonium sulphide, scrape off sufficient and examine as before.

Oxyhæmoglobin in solution with a little sodium chloride evaporated over sulphuric acid to syrupy consistence. Mixed with fifteen times its volume of glacial acetic acid and heated on a water-bath for several hours the mixture yields on cooling, flat rhombic crystals of hæmatin hydrochloride with dark violet colour and lustre—this is one of the recognised tests for blood stains.

The guaiacum test is highly spoken of. The stain must give a reaction with aqueous extract yielding no coloration to a straw-coloured solution of guaiacum in alcohol 90% when applied by itself, but a blue coloration within one second on further addition of hydrogen peroxide. Oxidisers and enzymes give a reaction with guaiacum solution *alone*. Blood does not.—*Analyst* 1912; *Yearb. Pharm.*, 1913, 40.

Chloral solution to extract blood stains. The stain is moistened with acetic acid and then soaked in a 70% to 80% solution of chloral hydrate for one or several hours if necessary. To the solution add a few drops of the reagent (guaiacum or benzidine), then add hydrogen peroxide 10 volume strength diluted with double volume of alcohol and slightly acidified with acetic acid (carefully superposed). The presence of pyridine greatly accelerates and intensifies the reactions.

Hæmochromogen Crystal Test. Reagent—Takayama's Solution 2 (an improvement on an earlier solution 1, used in 1912). Caustic soda solution 10% 3 ml., pyridine 3 ml., saturated grape sugar solution 3 ml., distilled water 7 ml. The solution keeps for one to two months.

Two or three drops are added to a small piece of the suspected material on a slide and covered with a cover glass. Salmon-pink crystals of characteristic appearance usually appear within 6 minutes in the cold. By warming the slide until bubbles just appear the crystals are formed almost at once. In the many types of stains tested the hæmochromogen crystals were readily obtained cold whereas in some cases hæmin crystals were not obtained at all, or only with difficulty.—D. J. A. Kerr and V. H. Mason, *Brit. med. J.*, i/1926, 134.

Kastle-Meyer Test. (Meyer's phenolphthalin reagent, as described under **Fæces**, is used.)

The technique consists in adding 10 to 20 drops of the reagent to the suspected blood-stained surface, then adding a few drops of fresh 20 vol. hydrogen peroxide. If blood is present, a deep permanganate colour develops almost immediately.

ne test is of value for detecting hæmoglobin.—J. Glaister, *Brit. med. J.*, 1926, 650.

Doubt as to reliability of the test. Aspirin and other drugs, also a red meat diet, may confuse. Cannot be accepted in a court of law.—D. Kerr, *Brit. med. J.*, i/1926, 721.

HÆMOGLOBIN DETERMINATION

Although the determination of the amount of hæmoglobin is one of the most important of all the chemical tests of the blood, yet as a rule it is the one which is determined with less care and by methods more inaccurate than those in use for any other constituent of the body. There are three methods in common use.

Carbon Monoxide Method. The Haldane modification of Gowers' method is the best known. The graduated tube is filled to the mark 10 with distilled water and 20 cu. mm. of blood added. The hæmoglobin is then converted to carboxyhæmoglobin by allowing a stream of coal gas to play over the diluted blood for a few minutes. Water is then added drop by drop until the tint of the standard tube is matched. The standards tend to fade and it is as well to have the instrument checked occasionally.

Acid Hæmatin Method. In the Sahli hæmoglobinometer and its modifications (Hellige, Newcomer, etc.) the blood is diluted with N/10 hydrochloric acid, which converts the hæmoglobin into acid hæmatin, which is a brownish suspension. This colour is more easy to match than that of whole blood and the necessity for a supply of coal gas (one of the disadvantages of the Haldane apparatus) is avoided.

The actual method of diluting the blood varies with different models. In some the graduated tube is filled to the mark 10 with N/10 hydrochloric acid, and 20 cu. mm. of blood collected in a pipette is added; then distilled water is added drop by drop until the tint of the standard tube is matched. In others the blood is collected in a special diluting pipette which is filled to the mark 1 with blood and then filled up to the mark 101 with N/10 hydrochloric acid, the pipette is then well shaken to ensure proper mixing and the contents of the pipette are run into a special rectangular cell. The standard is a movable wedge which is adjusted until the tints match.

Originally the standard was a solution of acid hæmatin, but this was found to fade badly and most instruments now employ a rod or wedge of coloured glass which is said to be permanent in colour.

It is important to remember that the colour of the solution of acid hæmatin gradually increases in intensity, and accordingly the reading should be made at a standard time after collection of the sample. (About 95% of the colour is retained in 10 minutes and after one-half to one hour the change is insignificant.) Further, as in all colour-matching procedures, readings should be made with a uniform source of light and, in making comparisons, several rapid readings should be made and the average of these taken; otherwise the eye will become fatigued and the reading will be erroneous.

Direct Method. This was the original method employed by Gowers, but most of the instruments are now, owing to their inaccuracy, only of historic interest. The only one in common use is the Dare Hæmoglobinometer, in which a thin film of undiluted blood is compared with a glass disc of graduated colour under standard lighting conditions: a reading can be obtained very rapidly, but the apparatus is costly and gives readings which are accurate to only 20%–30%.

Recently a photoelectric spectrohæmoglobinometer has been devised which gives very accurate results (*J. Lab. clin. Med.*, 1930, 15, 483), but its use is still limited to the laboratory, and the same applies to the oxygen capacity method of Van Slyke and the quantitative estimation of the iron content of the blood.—*J. biol. Chem.*, 1927, 74, 385.

ESTIMATION OF CORPUSCLES

One cubic millimetre of blood contains normally about 5,000,000 to 6,000,000 red corpuscles in man, and about 4,500,000 in woman. The average number of white corpuscles per cubic millimetre is about 7000 to 8000 in adults, and 10,000 in children.

The hæmacytometer chiefly used is the Thoma-Zeiss or Thoma-Hawksley.

This consists of a micrometer slide divided into 16 squares, each again being divided into 16 smaller squares. It has two pipettes, one for diluting the blood 1 to 100, for counting the red corpuscles, while the other which dilutes the blood 10 times is intended for estimation of the leucocytes. The number of red corpuscles seen in 4, 6, or if great accuracy is required, 16 (large squares, i.e., in 64, 96 or 256 smaller squares, is counted.

Estimation of Red Corpuscles. To ascertain the number in 1 cu.mm. of blood, knowing the volume of the cube standing on each small square to be $\frac{1}{400}$ cu. mm., *multiply the total number of red corpuscles counted by 4000 times the number of times of dilution of the blood, and divide the result by the number of small squares in which red corpuscles have been counted.* It is desirable to count the corpuscles touching and overlapping the two adjacent boundary lines of the left upper corners of the squares, but those on or overlapping the other two sides are excluded to compensate.

The normal dilution is 1 to 200; in polycythæmia 1 to 400; and in excessive anæmia 1 to 100 may be used. 5 or 6 corpuscles per square are a convenient number for counting.

The Thoma-Zeiss cell is $\frac{1}{10}$ mm. deep and each side of a small square is $\frac{1}{10}$ mm., hence the above figure $\frac{1}{400}$ cu. mm. as the volume of a small square.

The Burkner counting chamber, in which there are two rulings separated by an H-shaped moat, greatly facilitates filling the chamber, and the modified Neubauer ruling makes the actual counting much quicker and easier.

Gowers' Hæmocytometer Solution is still used as a diluent. Sodium sulphate 104 grains, acetic acid 1 drachm, distilled water 4 ounces. Filter.

Hayem's Solution is also employed. Sodium chloride 2, sodium sulphate 1, mercuric chloride 0.5, water 200.

Toison's Solution is also employed. It stains the leucocytes (see below).

Wright's Diluting Fluid for counting red corpuscles. Sodium chloride 1, mercuric chloride 0.2, distilled water to 100.

The "**Colour Index**" is the index of corpuscular richness. It is obtained by dividing the percentage of hæmoglobin by the percentage of red corpuscles. With the normal of red corpuscles as 5,000,000 and the hæmoglobin at 100 the index $\frac{100}{5000000} = 1$. In a case of red corpuscles 4,000,000 (=80% of normal) and hæmoglobin 40%, the index would be $\frac{40}{8000000} = 0.5$.

Estimation of Leucocytes may be conducted in a similar manner, by the Thoma-Zeiss instrument, but in this case it is desirable to stain them before counting by using Gowers' diluting fluid, with an appreciable addition of Löffler's methylene blue, or by Toison's Solution. (Dissolve methyl violet 5 g. in 0.025 g. in a mixture of glycerin 30 ml. and water 80 ml. Dissolve separately sodium sulphate 8 g. with sodium chloride 1 g. in water 80 ml. Mix and filter.) Leucocytes stain violet, red corpuscles greenish. For accuracy, count as many squares as possible.

A further formula for the staining fluid is solution of formaldehyde 1 g., sodium chloride 0.5, sodium sulphate 2.5, methyl violet 0.01, water 100.

Another method is to use a 3% aqueous acetic acid solution tinted with methylene blue or gentian violet as diluent; in this the red corpuscles become invisible while the leucocytes remain visible, and the blood need only be diluted 1 : 10 thus increasing the accuracy of the count.

Leucocytes, a Simple Method of Counting. To stain, a 3% sodium chloride solution deeply coloured with gentian violet is sufficient. It is simpler to count whole microscopic fields of known area rather than squares. Employing the 1 in 20 pipette, count whole microscopic field, not the squares, move the draw-tube of microscope into such position that $7\frac{1}{8}$ squares in diameter (Thoma-Zeiss scale) are in view. The cubic contents of this = $\frac{1}{100}$ cu. mm. Make a mark on the draw-tube—to be used for all occasions. Count twenty fields with above dilution, and add two cyphers to the number so obtained.

Total and Differential Count Simultaneously. By using Kristenson's fluid it is possible to perform a red and white count, a differential white count and a platelet count with one specimen of blood. The blood is diluted (1 : 2) in a pipette in the ordinary way with the following fluid:—sodium citrate 2.5 g., mercuric chloride 0.005 g., brilliant cresyl blue 0.5 g., water 250 ml. Before use it is mixed with an equal quantity of aqueous 5% urea. The leucocytes are so well stained that with a little practice a reasonably accurate differential count may be performed, but the platelet count will tend to be lower than actually is owing to the adhesion of platelets to the wall of the pipette.

BLOOD STAINING

To make films, prick patient's finger, press, let first drop of blood fall away, place the next drop (small) on the centre of a *really clean* $\frac{7}{8}$ in. square cover slip. Superimpose another and pull off so that the film is thin and even—not "ridges" and "valleys"—and dry in the air. No fixing is necessary, the methyl alcohol in the stain (Leishman, etc.) does this.

To Clean Cover Slips. Place the cover slips in pure nitric acid for 24 hours, stirring occasionally to ensure that the acid comes in contact with all the slips, wash in running water for the same time and keep in a well-stoppered bottle in spirit until required. Just before use the requisite number are removed from the spirit with forceps and dried either by burning the spirit off or by polishing with a piece of well washed linen.

The older methods of staining the films (Ehrlich's Triacid, Ehrlich's Triple Stain and Jenner's Stain) have been entirely superseded by Leishman's Stain and its modifications.

Romanowsky's Stain, Leishman's Modification. There are various modes of making and applying this stain. The following as suggested by Leishman gives the best results (the fixing and staining is done in one process so that fixing by heat is unnecessary):—

This is a solution in pure methyl alcohol of an eosin-methylene-blue-precipitation compound, 0.15 g. of the compound being dissolved in 100 ml. of methyl alcohol. (The methyl alcohol must be neutral in reaction and acetone-free.) The solution thus formed is a clear dark-blue liquid showing a green iridescence by reflected light. The stain is used by preparing films of blood in the usual way on clean cover glasses, and allowing to dry in the air. The films should be as thin as possible. Three or four drops of the stain are dropped on to the film and the cover glass is rotated, no attempt being made to check evaporation. After about half a minute six or eight drops of water are added, and allowed to mix by rotating with the stain, and staining is allowed to proceed for 5 minutes; in certain cases 10 minutes may be necessary. The film is now washed with distilled water, and a few drops of the water are allowed to remain on it for a minute. It is finally dried without heating and examined with an oil immersion lens.

The following results should be obtained:—Nuclei are stained a reddish-purple, cytoplasm tends to be very pale blue, neutrophile granules are a dirty pink, eosinophilic ones copper-red, basophilic ones metachromatic purple, and azurophilia is shown by a cherry-red colour, but only with specimens of the stain that have been stored for some time. Red corpuscles are copper-red unless they are polychromatic, when they are a dirty pink, but slight degrees of this are not shown by this stain. Blood platelets are purplish with reddish granules, malarial parasites stain blue with red chromatin granules (vide also malarial parasites this volume). Bacteria stain a light blue.

It is important that the distilled water employed should be neutral; if slightly acid, the eosinophile granules will stain very brightly, but the nuclei will be very faint; if alkaline, the red cells will be bluish and the cytoplasmic granules will not be stained. If there is difficulty in obtaining a satisfactory result the Haden Buffer solution described below can be used to replace the distilled water with advantage.

Pappenheim's Panoptic Method is to be recommended if very fine cytological detail is desired. Stain the air-dried films in May-Grunwald's stain face downwards in a covered vessel for 3 minutes; add an equal quantity of Haden's Buffer solution (6.63 g. of chemically pure crystalline potassium acid phosphate and 2.56 g. of anhydrous basic sodium phosphate dissolved in a litre of distilled water; this solution should have a pH of 6.4) and stain for a minute more; place the film without washing into the following solution:

Haden's solution, 5 ml.; Panchrom (or Giemsa's stain), 5 drops; orange-G-methyl green stain, 2 drops. Stain in this mixture for 6 to 12 minutes. (The orange-G-methyl green stain is prepared as follows: Equal parts of 1% aqueous solutions of orange-G and methyl green are mixed. The heavy precipitate that results is collected, dried and dissolved to saturation in pure methyl alcohol, and constitutes the stain.) The films are then washed in Haden's solution for 30 seconds and dried at room temperature. Distilled water may be substituted for Haden's solution throughout the technique but the results are not so good.

*Relative and Absolute Normal Leucocyte Counts
(per cu. mm.)*

Type of Cell	Per cent.	Absolute Number		
		Average	Minimum	Maximum
Total Leucocytes ..		7000	5000	10000
Myelocytes	0	0	0	0
Juvenile neutrophiles ..	4—8	400	200	700
Segmented neutrophiles	56—62	4200	2800	5800
Eosinophiles	1—3	200	50	300
Basophiles	0—0.75	35	15	75
Lymphocytes	20—30	2000	1000	3000
Monocytes	4—8	450	300	600

Blood counts. The conclusions of the orthodox hæmotologist when confronted by criticisms such as those of R. H. Simpson (*Brit. J. Radiol.* 1933, 6, 705) and G. W. Phillips were summarised by Prof. Eric Ponder and his collaborators in 1931 (*Quart. J. exp. Physiol.*, 1931-32, 21, 35) as follows: "Under conditions of moderate activity the large fluctuations in the total white cell count described by Sabin, Cunningham, Doan and Kindwall have not been observed. Those large fluctuations seem to be due principally to errors of method. The total white cell count shows, however, small fluctuations not exceeding $\pm 8\%$ throughout the day: these persist even after all errors of method have been allowed for." Until overwhelming evidence is produced that Prof. Ponder is wrong, it is safer to continue to assume a significance in pronounced variations of leucocyte counts, especially when dealing with workers in radiological departments.—*Lancet*, ii/1933, 1098.

Cooke Polynuclear Count. W. E. Cooke has simplified and improved the original Arneth leucocytic index, and the method is often of value, particularly in judging the progress of a disease. One hundred consecutive neutrophile polymorphonuclears are counted and arranged in groups according to the number of nuclear lobes. These groups are then expressed as percentages of the neutrophiles, not of the total leucocytes. The normal figures for the number of cells in each class is as follows: Class I 10%, Class II 25%, Class III 47%, Class IV 16%, Class V 2%. For the significance of changes in the count and the exact definition of what is meant by a lobe see *The Polynuclear Count* by W. E. Cooke and Eric Ponder.

The Schilling Hæmogram divides the neutrophiles into myelocytes, metamyelocytes (nucleus indented or S-shaped, basi- and oxy-chromatin clearly differentiated), stab forms or juvenile neutrophiles (nucleus ribbon-like and twisted, or sausage-shaped, but pyknotic), and mature segmented forms. The numbers of the different types are then expressed as percentages of the total leucocytes in contrast to the Cooke index. The information obtained is different from that in the Cooke-Arneth index, as the more immature granular cells are studied in greater detail, but the number of lobes in the segmented forms is ignored, and certain hæmatologists have questioned the Cooke-Arneth criteria for judging the maturity of the neutrophile whereas Schilling's grouping is unquestioned.

Oxydase Reaction. In certain cases of leukæmia the oxydase reaction may be of assistance, but it is important to recognise that myeloblasts, lymphoblasts and all the cells of the lymphoid series are oxydase-negative, the premyelocyte, myelocyte and mature granular cells are oxydase-positive, and monocytes may be oxydase-negative or show a few granules in the cytoplasm. The most reliable method is that of Bryce. Two solutions are used: (A) 0.3 g. benzidine base, 1 ml. of a saturated aqueous solution of sodium nitroprusside; ethyl alcohol 100 ml. (B) 0.5% solution of hydrogen peroxide. Air-dried blood films are treated with the solution A for 1 minute, then an equal quantity of solution B is added and allowed to act for a further 3 minutes; the films are then washed for 10 minutes and allowed to dry in air. They may then be counterstained with Leishman, but the dilute stain should be allowed to act for at least 10 minutes.

Punctate Basophilia and Polychromasia. In cases of suspected lead poisoning it is often important to detect the slightest degree of punctate basophilia, and the ordinary eosin-methylene blue stains fail to do this; accordingly the method of Manson-Schwarz is employed. Two solutions are required: (A) boric acid 2 g., methylene blue 1 g., distilled water (carbon-dioxide-free) 100 ml.; (B) 0.28% sodium hydroxide in boiled distilled water. Immediately before use, 6 drops of solution A are mixed with 8 drops of solution B and made up to 10 ml. with boiled distilled water. Air-dried blood films are fixed in methyl alcohol for 5 minutes, washed with distilled water and then placed in the stain for 5 seconds; washed with distilled water, dried in air and mounted.

Reticulocytes. The presence of reticulated red cells can only be determined in unfixed blood by means of supravital staining. There are normally 0.5 to 1% in the circulating blood, and their study is of value in judging the response to treatment in the anæmias. Perfectly clean grease-free slides should be slightly warmed, and a drop of a 0.3% solution of brilliant cresyl blue in absolute ethyl alcohol applied. If the slides are clean the stain will spread out in an even ring and dry quickly. (A large number may be prepared at one time and will keep indefinitely if kept dust-free.) When the count is to be made, a small drop of blood is collected on a grease-free cover slip and placed on the ring of stain on the slide. The cover slip is ringed round with soft paraffin to prevent drying, and may be examined in 10 minutes. The reticulated red cells are expressed as a percentage of the red cells.

Vital Staining of the Leucocytes by Janus green B and neutral red is a complicated laboratory procedure, and readers must be referred to the papers of Sabin and Simpson for details of the technique.—*Bull. John Hopkins Hosp.*, 1923, 34, 277, *et seq.*

Determination of the Size of the Red Cell. In the Price-Jones Curve the diameters of 500 red cells in a stained blood film are measured, either by projection on to a screen or by means of an eyepiece micrometer, and the results plotted in the form of a graph. From this may be determined the mean diameter of the red cells and the degree of variation in the size of individual cells. The normal mean diameter is 7.2 microns. The method is laborious but there is no other way of obtaining the information it gives.

The Hæmatocrit is a simple and reliable method of determining the average volume of the red cells. There are many methods employed, but the most satisfactory is that of Wintrobe. In this a narrow glass tube of even bore, and etched with a centimetre-millimetre scale 10 cm. in length, is filled exactly to the 10 mark with oxalated venous blood. (10 mg. of potassium oxalate will prevent the coagulation of 5 ml. of blood. This causes a shrinkage in cell volume of approximately 5% which must be corrected for in the final result.) The tube is then centrifuged at 3000 revolutions per minute for about 30 minutes, and the volume of packed red cells read off the scale. This is normally 42.4 ml. per 100 ml. of blood. Further, if a total red cell count is performed at the same time it is possible to determine the average corpuscular volume, which is normally 80 cu. microns. For a more detailed description and an account of the other factors which may be deduced, such as the volume index, the mean corpuscular thickness and the mean corpuscular volume, the reader is referred to a paper in the *American Journal of Clinical Pathology*, i/1931, 147.

The Halometer devised by Young, is based on the diffraction method of measuring small particles and although the measurements by this method are readily performed, they yield average figures only and therefore afford no information which cannot be derived as readily and much more accurately from a hæmatocrit.

Reliability of the halometer.—A. Pijper, *Lancet*, i/1934, 483.

A comparative study of red cell diameter and red cell volume measurements.—J. M. Vaughan and H. M. Goddard, *Lancet*, i/1934, 513.

Examinations Concerned with Coagulation

Enumeration of the Blood Platelets. Unless special precautions are taken to prevent adhesion and destruction of the platelets, counts done by direct methods tend to give low readings; accordingly only indirect methods will be described, in which the proportion of platelets to red cells is determined and from a red cell count performed at the same time the absolute platelet count is calculated. The normal average platelet count is 300,000 per cu. mm.

Fonio's Method. A drop of 14% magnesium sulphate is placed on the skin of the finger which is pricked through this. The blood, which wells up through this, is diluted and clumping of the platelets prevented. A smear is made from this diluted blood and is stained in the usual way with Leishman's stain. It is sometimes an advantage to overstain slightly so that the platelets may be seen clearly.

Another method is that of Rees and Ecker in which the finger is pricked through a drop of the special diluting fluid (sodium citrate, 3.8 g.; formalin, 0.2 ml.; brilliant cresyl blue, 0.1 g.; distilled water, 100 ml. Filter before using.) and a drop of the diluted blood is placed on a slide, covered with a cover slip and examined wet and unfixed.

Coagulation Time. The Dale and Laidlaw Coagulation Tube is the apparatus most commonly employed. This consists of a standard sized capillary tube which is slightly lipped at each end so as to allow free entry of blood, and at the same time to retain a small lead shot which is free to roll from one end of the tube to the other.

The tube is filled with blood by capillary attraction and transferred to a water-bath at 87° where it is held by a special pair of forceps which occlude the open ends. It is then tilted up and down until the travel of the lead shot is just arrested by the process of coagulation. The time taken between the first appearance of the blood and the arrest of the lead shot is the coagulation time and is normally two minutes by this method. It is greatly prolonged in hæmophilia. A rather more satisfactory instrument is Gibbs' Coagulometer described in the *Quarterly Journal of Medicine*, 1923-4, xvii, 312.

Bleeding Time (Duke's Method). The lobe of the ear or finger is pricked so that the blood flows easily drop by drop without any assistance; each drop is removed with filter paper as it forms until the bleeding stops, care being taken not to touch the skin. The time interval between the appearance of the first drop and the removal of the last represents the bleeding time. Normally it is two or three minutes and is greatly prolonged in most purpuric conditions.

Capillary Resistance Test (Rumpel - Leede Phenomenon). If a sphygmomanometer arm band adjusted to a pressure just above the diastolic is left on the arm for 3 to 10 minutes, a crop of petechiæ will appear distal to the tourniquet in those hæmorrhagic states in which there is abnormal capillary permeability.

Fragility of the Red Cells. The resistance of the red cells to hypotonic salt solutions is usually determined by the method of Sanford. Twelve small test-tubes are set up, and into each is placed an equal amount of a solution of sodium chloride ranging from 0·3% to 0·9%, each tube differing by 0·05%. A drop of blood is put into each tube and mixed with the salt solution. In 2 hours the results are read. Commencing hæmolysis is indicated by a slight reddish colouring which has resulted from the laking of the least resistant cells. Complete hæmolysis is indicated by a clear red solution and the absence of any corpuscular residue on shaking the tube. Normally hæmolysis commences at 0·45% and is complete at 0·35%. Increased fragility is found notably in hæmolytic jaundice, and decreased fragility in certain forms of splenic anæmia.

Sedimentation Rate of the Red Cells. A great number of methods are used in carrying out this test, but the principle is the same throughout. Venous blood is collected with an anticoagulant and placed in a graduated tube held vertically, and the distance the cells have sedimented noted at timed intervals. Normally the rate of sedimentation is relatively slow, but in the blood from a patient with any active disease the rate is greatly increased. It is important to make a correction for the actual red cell count, as this is liable to produce considerable errors. It is important to recognise that the sedimentation test is in no sense a diagnostic test, but will merely indicate the degree of activity of a chronic disease.

Blood Grouping. Standard grouping sera of Groups II and III must be obtained. They should be kept in a refrigerator, but stale sera should never be used, as the agglutinating titre may have fallen to a negligible figure and fallacious results be obtained. A small quantity of each serum is placed on a white tile and each is marked with its group. A small quantity of the patient's blood is added to each serum and thoroughly mixed so as to give the sera a definite pink tinge. The results are read in 10 to 15 minutes. A variety of events may occur.

1. Both Group II and Group III sera become stippled (i.e. show agglutination)—Patient is Group I.
2. Both sera show no change—Patient is Group IV.
3. Group II serum takes on a stippled appearance, Group III serum is unchanged—Patient is Group III.
4. Group III serum takes on a stippled appearance, Group II serum is unchanged—Patient is Group II.

In addition, before a transfusion is performed, it is most important to perform a direct cross-grouping in a similar manner between some of the patient's blood serum (obtained from clotted blood) and the donor's blood. If any stippling or agglutination should appear another donor must be found who is compatible. If no grouping sera is available to determine the patient's group, the cross-grouping may be done alone, as it does not matter to what group either donor or recipient belong, provided they are compatible one with the other.

Blood Volume. Methods of determining blood volume in use at the present time are based on the principle that, by the addition of a definite quantity of a known substance to the circulation, the total quantity of blood may be calculated from the concentration of the foreign substance in a sample of blood. The carbon monoxide and the congo red method, or a combination of the two, are now most generally employed. By the former method the saturation of the red cells of an individual to whom a certain amount of carbon monoxide has been administered, is determined and the total quantity of blood is estimated from the relative quantities of red cells and plasma as determined by means of the hæmatocrit; in the dye method the plasma volume is first determined from the dilution of a given quantity of dye injected into the blood, and the total quantity of blood is then estimated from hæmatocrit values.

The total blood volume varies with the height, weight and particularly the surface area of the body, and values vary between 4000 ml. and 8000 ml. in normal adults. A full account of the methods and the changes in disease will be found in the monograph by Rowntree on the subject.

Action of certain compounds on blood platelets and leucocytes, when injected intravenously in rabbits:—

	Blood Platelets	Leucocytes
Calcium chloride	Transient reduction	Increased
Sodium citrate	Transient reduction	Considerable decrease
Physiol. salt solution	Not affected	Not affected
Epinephrine	Increased	Unchanged or increased
Histamine	Increased	
Nicotine	Decreased	
Acetylcholine	Increased	Not affected
Pilocarpine (toxic doses)	Not affected	Slightly increased
Atropine	Marked diminution	Increased

—C. R. Acad. Sci., Paris, per J. Amer. med. Ass., ii/1925, 856.

Hydrogen-ion Concentration of the Blood

The reaction of the blood serum varies approximately between pH 7 and pH 8, the neutral point, pH 7, being reached only in severe uncompensated acidosis and a reaction of pH 8 being attained perhaps only after administration of alkalis.

A series of Standard Solutions is required, of known pH, to be used in conjunction with a delicate indicator which will show easily recognised changes in colour due to hydrogen-ion concentrations approximating that of the solution tested. In the case of blood, colouring matter and proteins must be excluded by dialysing.

Collodion Sacs are employed. Blood dropped into these and dialysed for five minutes is free from interfering bodies but contains salts which are responsive to phenol red—an indicator showing differences in tint between pH 6·4 and 8·4.

The following solutions are first prepared:—

A. M/15 **Potassium Acid Phosphate** (KH₂PO₄) **Solution.** (9·078 g. per litre of fresh distilled water.)

B. M/15 **Sodium Phosphate** (Na₂HPO₄·12H₂O) **Solution.** (23·880 g. per litre of fresh distilled water.)

Mix solutions A and B as follows:—

pH	6·4	6·6	6·8	7·0	7·1	7·2	7·3	7·4	7·5	7·6	7·7	7·8	8·0	8·2	8·4
A	73·0	63·0	51·0	37·0	32·0	27·0	23·0	19·0	15·8	13·2	11·0	8·8	5·6	3·2	2·0
B	27·0	37·0	49·0	63·0	68·0	73·0	77·0	81·0	84·2	86·8	89·0	91·2	94·4	96·8	98·0

Place 3 ml. of each of the mixed solutions in 100 mm. by 10 mm. test-tubes, add 5 drops of 0·01% phenol red to each and seal off the tops. The series of colours so prepared represents different concentrations of hydrogen ions within limits likely to be found.

Collodion Sacs. The collodion is directed to be made by dissolving 1 oz. of pyroxylin in ether 250 ml. and alcohol 250 ml. Allow to deposit and use the supernatant solution.

A good piece of glass tubing sealed off like a test-tube with internal diameter 9 mm. by 120 mm. is used as a mould. Fill it with the collodion, invert it and pour out half the contents. Then place it upright and allow the collodion to fill the lower half again. Invert a second time and rotate on its vertical axis, the collodion being drained off. This must be done to render even. Now clamp the tube inverted, allow to stand 10 minutes, and soak bodily in water for 5 minutes. Loosen the upper rim with a knife and run a little water between the sac and the tube, gradually pull out the sac, and preserve under water.

To Conduct the Determination:—

The assay must be done in a room free from fumes of acids or ammonia.

Place 1 to 3 ml. of clear serum or of the blood to be tested in a sac which has been washed inside and out with 0.8% sodium chloride solution—the sac having been previously tested for leaks by filling it with the salt solution.

Lower the sac into a test-tube 100 mm. by 10 mm. inside diameter containing 3 ml. of the salt solution until the fluid outside is as high as on the inside. Dialyse for 5 to 10 minutes. Remove the sac and add 5 drops of the indicator, mixing thoroughly with the dialysate, and compare colour with the set of standards against a white background.

The limits of error are very slight. The same results are obtained with 1 ml. or 3 ml. of blood, and it is immaterial whether there is 1 ml. or 3 ml. of salt solution. A mild case of acidosis gave an average of 7.55 on repeated examination, using serum, and the oxalated whole blood from the same case gave an average of 7.25.

Reactivity of the blood in relation to cardiac breathlessness, surgical shock, etc. The “strip” of variation in acidity or alkalinity of the plasma of the blood within which life is possible is a very narrow one, and it suffices to render the medium within which living cells are situated acid or alkaline to the feeble limit of one-thousandth normal, or less, in order to destroy life. Blood plasma is capable of neutralising large amounts of either acid or alkali without itself being or becoming markedly acid or alkaline. A consideration of the variations in the property of balanced alkalinity and acidity.—Benjamin Moore, *Brit. med. J.*, ii/1918, 251; cf. Prof. Bayliss, *ibid*, 78.

An account of the reaction and “buffers” of the blood—A. V. Hill, *Brit. med. J.*, i/1922, 340.

The acid-base equilibrium of body-fluids. A revised nomenclature. The Hæmoglobin Committee of the Medical Research Council have issued a standardised nomenclature based on hydrogen-ion concentration.—*Lancet*, i/1923, 613.

H-ion concentration higher inside than outside the red blood corpuscle. Carbon dioxide is not carried in the blood as a substance adsorbed to the hæmoglobin, but as a part of a physico-chemical system involving the sodium bicarbonate present.—*Rep. med. Res. Coun., Lond.*, 1923-4.

Alkali Reserve of Blood. This corresponds to the plasma bicarbonate, and is measured as the amount of CO_2 , at N.T.P., which is expelled from 100 volumes of plasma which has been in equilibrium with alveolar air at room temperature.—D. D. Van Slyke and J. J. Neall, *J. biol. Chem.*, 1924, 61, 523.

Uric Acid in Blood. Uric acid in blood is raised in nephritis. In uræmia it may reach 20 mg. per 100 ml. The general opinion is that hyperuricæmia is present in the blood in the toxæmia of pregnancy. It is increased in hypertension and arterio-sclerosis and a high blood uric acid is found in most cases of leucæmia.

During pregnancy and delivery rather low values for uric acid in the blood were found, the average being 2.74 mg. per 100 ml.; may increase slightly after delivery. In eclampsia, uric acid is always considerably decreased.—*J. Amer. med. Ass.*, ii/1925, 861.

Uric acid content of blood serum and of corpuscles is twice as great in gouty conditions as in normal health.—*J. chem. Soc. Abstr.*, i/1922, 1086.

Folin's revised method for determination of uric acid in blood.—*J. biol. Chem.*, 1922, 54, 153.

See also Benedict and Behre. Determination and distribution of uric acid.—*J. biol. Chem.*, 1931, 92, 161.

Calcium and other Inorganic Elements in Blood.

Estimation of Calcium in Blood. 2 ml. of ammonium oxalate solution (3·5%) is measured into a centrifuge tube, having a steep conical end, 1 ml. of serum is added and the contents stirred vigorously. Allow the tube to stand 2 to 3 hours and then centrifuge at 3000 revs. per minute for 10 minutes. Pour off supernatant fluid and drain tube over filter paper. Add a further 2 ml. of ammonium oxalate solution, centrifuge, pour off, and repeat with a fresh 2 ml. as before. Dry the precipitate by heating the centrifuge tube in the steam oven and convert the calcium oxalate into carbonate by passing the tube through a bunsen flame for one minute, any ammonium oxalate left being converted into ammonium carbonate and volatilised. After cooling, 1 ml. of N/100 phosphoric acid is added and, when solution is complete, one drop (0·016 ml.) of 0·04% bromophenol blue is added and titration carried out with N/50 sodium hydroxide using a micro-burette or micrometer syringe. The end-point corresponds with a colour intermediary between those of buffer solutions of pH 4·0 and 4·2, and the difference between the titration figure so obtained, and that for the acid alone gives the amount of calcium in the serum taken. 1 ml. only of the serum need be taken, and results within 5% of the correct value have been obtained with 0·01 mg. of calcium per ml.—J. W. Trevan and H. W. Bainbridge, *Biochem. J.*, 1926, 423-426.

1 ml. of N/100 phosphoric acid is equivalent to 0·64 mg. of calcium oxalate or 0·2 mg. of calcium. Thus, 0·1 mg. of calcium which is a little more than the average content per ml. of serum, would combine with 0·5 ml. of N/100 phosphoric acid.

Method of Kramer and Tisdall. The calcium is precipitated from serum by means of ammonium oxalate. The precipitate is centrifuged and washed with weak ammonia and after solution in dilute sulphuric acid the calcium oxalate is titrated with N/100 KMnO_4 .—B. Kramer and F. F. Tisdall, *J. biol. Chem.*, 1921, 47, 475, and 1923, 56, 439.

The average serum-calcium value in normal children was found to be 10·4 mg. per 100 ml. and in cases with inflamed tonsils and adenoids but good muscle tone, 9·8 mg. as average. The average in cases with marked lack of muscle tone was 9·0 (range 6·6 to 10·6). Inorganic phosphates of the plasma in all cases were approximately normal, though the calcium values in the group with marked lack of muscle tone were more variable than the normal and groups with inflamed tonsils and adenoids but good muscle tone; no relationship between calcium level in the blood and muscle hypotonus was established.—L. Wills, *Brit. med. J.*, i/1925, 302.

Hypercalcaemia. High blood calcium figures are found in cases of parathyroid tumour and with excessive administration of parathyroid extract. The blood calcium figure is sometimes raised in cases of gout and cholelithiasis.

Hypocalcaemia. Low blood calcium figures found in tetany due to deficient parathyroid secretion or after parathyroidectomy: also in advanced azotæmic nephritis. Low figures sometimes found in renal rickets and chronic sepsis. When blood calcium is normal it is not possible to raise it by oral administration of calcium.

Potassium Content of the Blood. Normal human serum contains somewhat less than 20 mg. of potassium per 100 ml., while whole blood contains from 8 to 10 times that amount.—Myers and Short, *Yearb. Pharm.*, 1922, 36.

A Method of Estimation is provided, 18th Edn., Vol. II, p. 402.

Mean content was 20·3 mg. per 100 ml. An increase was found at the beginning of menstruation.—*Brit. chem. Abstr. A.*, 1928, 913.

The inorganic constituents of the blood.—O. L. V. de Wesselow, *Lancet* i/1924, 1099.

Bound phenols found in every normal blood in concentration of about 0·05 mg. per 100 ml. Large amounts and *free phenols* in pernicious anæmia and a remarkable increase in the insufficiency stage of nephritis.—*J. Amer. med. Ass.*, ii/1925, 1681.

Chemical tests of the blood—indications and interpretations with a collection of clinical aphorisms.—R. Rockwood, *J. Amer. med. Ass.*, ii/1928, 157.

BLOOD SUGAR ESTIMATION

Generally speaking, in health, the amount of blood sugar lies between 0.09% and 0.11%, except soon after a meal. With normal individuals, the ingestion of 50 g. of glucose in 150 ml. of water causes an increase, even to 0.18%, but the concentration falls back to normal in about 90 minutes. With diabetic patients there is usually a greater increase, but of more importance in diagnosis is a characteristic delay, often of many hours, before the sugar decreases to the usual value.

Comparative determinations of blood sugar show that different values are obtained for blood in different parts of the circulation. It is suggested that blood is richer in sugar when circulating through active parts, and this is supported by the fact that blood from a paralysed limb is poorer in sugar than that from other parts of the body.—L. Pincussen and N. Klissunis, *Biochem. Z.*, 1924, 150, 44, per *J. chem. Soc. Abstr.*, i/1924, 1124.

In diabetic patients improving clinically it was found that the effect of the same dosage of insulin was a more immediate, but smaller, drop in percentage of blood sugar, and the sugar started to increase in a shorter time after the injection. Subjects who showed a slight reaction to epinephrine tended to give a relatively marked response to insulin.—R. S. Lyman, E. Nicholls and W. S. McCann, *J. Pharmacol.*, 1923, 365.

Diabetic sugar thought identical with normal blood sugar.—*Rep. med. Res. Coun., Lond.*, 1923-4.

The blood sugar in cases of epilepsy.—I. De Burgh Daly, J. Pryde and J. Walker, *Brit. med. J.*, i/1924, 232.

Renal Glycosuria. A glucose tolerance test shows a low or normal blood sugar curve but is accompanied by glycosuria. There is a lowering of the renal threshold which is not of pathological significance and no treatment is required.

Glycolysis. Sugar tends to disappear slowly from drawn blood and unless the blood is to be examined immediately some form of preservative must be used. For this purpose a mixture of sodium fluoride 1 g. and thymol 0.1 g. is the most suitable. It is used in the proportion of 0.1 g. to 10 ml. of blood. It acts both as an anti-coagulant and preservative. Arterial blood has a slightly higher figure than venous blood and therefore blood collected by finger or ear prick will show a sugar content of a few mg. % above that in blood collected by vein puncture.

Blood sugar can be determined by colorimetric or titration methods. The latter have the advantage of not requiring expensive apparatus.

Maclean's Method.—0.2 ml. of the blood is mixed with 23.8 ml. of a solution containing 15% of sodium sulphate and 0.1% (v/v) of acetic acid. After raising to boiling and removing from the flame, 1 ml. of dialysed iron solution is added, and, when cooled, the mixture is filtered through a Whatman paper, 20 ml. of the filtrate being transferred to a 100 ml. conical flask. 2 ml. of standard copper solution (see below) is added and the mixture boiled for 6 minutes, cooled, and acidified with 2 ml. of 25% sulphuric acid. In one minute the liberated iodine is titrated with fresh N/400 sodium thiosulphate, using two drops of 1% soluble starch solution towards the end. The standard copper solution is also similarly titrated against N/400 thiosulphate by adding 2 ml. of 25% sulphuric acid to a mixture of 2 ml. of the copper solution and 5 ml. of the acid sodium sulphate solution.

The difference between the two titration readings gives the ml. of thiosulphate due to the sugar, and the percentage is read off from a table (v. *Modern Methods*

in *Diagnosis and Treatment of Glycosuria and Diabetes*.—Maclean), or the amount can be calculated thus:—

$$\% \text{ sugar} = (A \times 0.049) + 0.012$$

where A = (ml. of N/400 thiosulphate per 2 ml. of copper solution — ml. N/400 thiosulphate in experiment).

THE STANDARD COPPER SOLUTION. Should stand a few days before use. Potassium bicarbonate 12 g. is dissolved by gentle heat (not above 37°) in about 60 ml. of distilled water and potassium carbonate (anhydrous) 8 g. added. Copper sulphate (cryst.) 0.35 g. dissolved in a little water, is mixed with this, and when effervescence is over, after warming, if necessary, to dissolve any insoluble carbonate, potassium iodate 0.05 g. and potassium iodide 0.50 g. are added. The solution is then filtered through a starch-free paper and adjusted to 100 ml. When titrated as described, 2 ml. should require about 11 ml. N/400 thiosulphate.

For accurate work, the heating of this solution and the blood filtrate should be ensured by using the same burner and gas-pressure to bring the 22 ml. solution in the flask to vigorous boiling in 100 seconds.

The Cole Modification of the Maclean method, using metaphosphoric acid as protein precipitant, does not seem to possess any distinct advantage over the original method being found entirely satisfactory.—G. R. Lynch, *Lancet* i/1923, 1180.

In adapting **Cole's Method** of estimating blood sugar to the slightly different conditions in the case of urine, no marked deviation from Cole's procedure is necessary, but strict adherence to technique is essential. 1. The interfering substances are removed by mixing equal volumes of urine and Patein and Dufau's reagent, rendering slightly alkaline with solid sodium bicarbonate and filtering. A slight excess of sodium sulphide solution is added to 10 ml. of the filtrate, which is then made up to 100 ml. and filtered. 1 ml. of this filtrate will be equivalent to 0.05 ml. of the urine. (**PATEIN AND DUFAU'S REAGENT**: Dissolve by heat red mercuric oxide 220 g. in conc. nitric acid 160 ml., and water 160 ml. Cool, add 75 ml. of N/1 sodium hydroxide and make up to 1 litre.) 2. Determine approximately the sugar in the original urine by Benedict's, Nylander's, Fehling's, or Crismer's safranin reagent, and take of the second filtrate quantities (ranging from 2 to 10 ml.) inversely proportional to the amount of sugar indicated, which would probably lie between 0.08% and 0.15%. 3. To this amount add 3 ml. of Cole's alkaline copper iodate mixture and make up to 23 ml. with water. Heat so that the solution boils in 2 minutes, and after boiling for exactly 8 minutes run in 5 ml. of *B.P.* dilute sulphuric acid, and remove flask from flame. Allow to cool, add 2 drops of potassium iodide solution 10%, and estimate free iodine with N/200 sodium thiosulphate, using micro-burette and starch as indicator. The difference between the number of ml. of this used in the titration, and in a blank experiment with the alkaline copper iodate mixture gives the "thiosulphate deficiency," from which can be calculated the % of reducing sugars present in the original urine, 1 ml. of the thiosulphate solution being equivalent to 0.035% reducing sugars, according to the table provided. (**COLE'S ALKALINE COPPER IODATE MIXTURE**: potassium bicarbonate 20, potassium carbonate 30, copper sulphate 0.875, potassium iodate 0.075, water to 250.) The urine examined should be from a 24-hour sample, preserved if necessary with toluene.—F. Wokes, *Pharm. J.*, ii/1925, 127.

The Folin and Wu Colorimetric Method (*J. biol. Chem.*, 1919, 38, 8, and 1920, 41, 367). This requires 0.2 ml. of blood, and consists of a protein precipitation with tungstic acid and estimation of the sugar with phosphomolybdic acid. Mackenzie Wallis and Gallagher applied the use of the torsion balance to this process, the blood being soaked up into a piece of filter paper weighed before and after impregnation.—*Lancet*, ii/1920, 784.

The micro-method of Folin and Wu as adapted by Wallis and others is the most suitable for routine work.

Method of Hagedorn and Jensen. This is a micro-titration method, and if pure potassium ferricyanide is used gives very accurate results.

Both these methods are described in Harrison's *Chemical Methods in Clinical Medicine*.

Folin's Blood Tube. This is 20.5 cm. long and 2.3 cm. wide in the upper portion of 14 cm. Below this, its width is constricted to 0.9 cm. for 4 cm. length and terminates in a bulb about 2 cm. wide. Its capacity is 25 ml.

Calvert's Modification is founded on the above methods. The blood is collected in a small platinum capsule and weighed on a torsion balance. After removal of protein, and treatment with alkaline copper solution, phosphomolybdic acid is added. Unreduced copper is decolourised and the cuprous oxide present dissolves, giving a deep blue solution, the colour being proportional to the sugar originally present. This solution is compared in a colorimeter with standard blue glass discs. It is claimed that the accuracy of the method is high.—*Biochem. J.*, 1923, 177. See also *Brit. med. J. Epit.*, i/1925, 10.

Kramer and Gittleman's Modification of Folin and Wu's method is simple—only 0.05 to 0.1 ml. of blood required. The blood is drawn into a fine pipette and mixed with 1.5 ml. of distilled water. Proteins are precipitated by adding 0.1 ml. of 10% sodium tungstate solution followed by 0.1 ml. of $2/3N$ H_2SO_4 . This is well mixed, allowed to stand and centrifuged. The supernatant liquor is pipetted off and transferred to a Folin-Wu tube. Two controls are prepared with standard sugar solution, alkaline copper solution is added to all three, the tubes are heated, and 2 ml. phosphomolybdic acid solution added to each. The contents are mixed and the colour compared. A calculation shows the sugar in mg. per 100 ml.—*Pharm. J.*, i/1924, 140.

The blue colour given by phosphomolybdic acid and cuprous oxide fades in time, and therefore colorimetric measurements must be made within an hour. Calvert's method criticised.—R. V. Stanford and A. H. H. Wheatley, *Biochem. J.*, 1924, 22.

Resorcinol Method. Colorimetric assay by yellow colour given on boiling for 1 hour with 20% hydrochloric acid and excess of resorcinol.—I. B. Glassmann, *Hoppe-Seyl. Z.*, 1925, 120, 16.

Time-saving points in the estimation of glucose—use of **Dreyer's Pipette** (an ungraduated pipette which drops very consistently 22 to 24 drops of water to the cubic centimetre).—F. T. Grey, *Brit. med. J.*, i/1925, 502.

Criticism of modern methods of blood sugar determination and a description of a micro-method for the determination of true sugar by a modified Folin-Wu method.—F. K. Herbert and M. C. Bourne, *Brit. med. J.*, i/1931, 94.

CEREBROSPINAL FLUID

The composition is virtually that of Locke's Modification of Ringer's Solution. In examining a specimen, centrifuge or allow to stand for any sediment to deposit. Examine sediment for cells and bacteria. Inoculate broth and other media for bacteria.

Normal cerebrospinal fluid is a clear colourless fluid with no clot and should have the following characteristics:

Reaction: faintly alkaline.

Cells: Not more than 5 per cu. mm.

Total Protein: 10 to 35 mg. per 100 ml.

Globulin test: Negative.

Sugar: 40 to 80 mg. per 100 ml. (The sugar content will vary with the level of the blood sugar).

Chlorides (as NaCl): 700 to 750 mg. per 100 ml.

Urea: 10 to 40 mg. per 100 ml. This will vary with the blood urea.

If the fluid contains a clot this indicates the presence of fibrinogen and is always of pathological significance unless blood has been admixed at the time of the lumbar puncture. If the fluid is red the colour is due to blood. Red blood cells may be detected in the centrifuged deposit of an apparently colourless fluid. A yellow fluid is due to bilirubin formed from the hæmoglobin of a previous hæmorrhage.

Estimation of Total Protein. This is best carried out by Mestrezat's method. The protein is precipitated by 30% trichloroacetic acid and the resulting turbidity is compared with a series of standard protein solutions similarly treated. (See Harrison's *Chemical Methods in Clinical Medicine* for full description). Nearly all pathological fluids show an increase of protein. This increase of protein may or may not be accompanied by an increase of cells. Bacterial infection usually results in an enormous increase of cells. When there is a block in the subarachnoid space the protein content may be very high. A high protein content without an equivalent cell increase is known as *Froin's syndrome*. This occurs in tumours of the cord, spinal caries and chronic meningitis.

Qualitative Test for Globulin. The test usually employed is that of adding a small quantity of cerebrospinal fluid to an equal quantity of saturated ammonium sulphate. After shaking, normal fluids remain clear or show only the faintest degree of opalescence. An increased globulin content is always pathological if there is no blood present in the specimen. Protein figures and globulin tests in a specimen containing blood are of no value. The chief value of the globulin test is in syphilitic lesions where although the total protein may be only slightly increased the globulin ratio is so raised that definite positive reactions are obtained.

Sugar. This varies with the blood sugar, but tends to lag a little behind. In acute meningitis the sugar is often lowered.

Chlorides. These may be estimated by direct titration with N/50 AgNO_3 using potassium chromate as the indicator. High figures are not often met with but occur in advanced cases of renal inefficiency. Low chloride figures are found in meningitis. Chloride estimations are particularly valuable in the early diagnosis of tuberculous meningitis, as the figures in this disease are usually very low, between 500 and 650 mg. Any factor tending to lower the blood chloride may cause a fall in the chloride content of the cerebrospinal fluid.

Urea. This always bears a close relationship to the level in the blood, though tending to be a little lower. There is no special value in estimating the spinal fluid urea in cases of suspected uræmia.

Sugar and urea may be estimated by the methods employed in the analysis of blood.

Differential Diagnosis of Syphilitic from Parasyphilitic Affections by Examination of Cerebrospinal Fluid.

Normally, the fluid is practically free from corpuscular elements; from 1 to 5 lymphocytes may be seen in the centrifuged deposit in the ordinary microscopic field. In acute microbic infections of the cerebrospinal meninges leucocytosis occurs, mostly of the polynuclear type.

In certain more chronic affections, as in tuberculosis, trypanosomiasis and syphilis, excess of leucocytes also occurs—mostly *mononuclear*, i.e., there is a lymphocytosis or pleocytosis. Tubercle bacilli and trypanosomes can usually be found, but the *Sp. pallida* has not been found. The pleocytosis of cerebrospinal syphilis, tabes and general paralysis is often a very early occurrence of great diagnostic value.

In florid syphilis and in cerebrospinal syphilis as well as in tabes and general paralysis, the Wassermann reaction is practically always +.

The second reaction in *diagnosis of parasyphilitic affections* is the finding of an excess of globulin. In combination with a + Wassermann reaction and pleocytosis it is pathognomic of parasyphilis.

The third reaction is the pleocytosis; the fourth is the Wassermann reaction both already mentioned. The four reactions are relied upon for diagnosis.

Routine examination of cerebrospinal fluid in syphilis.—C. H. Mills, *Brit. med. J.*, ii/1927, 527. See also J. G. Greenfield, *Lancet*, ii/1928, 716.

Colloidal Gold Reaction. Zsigmondy found that certain colloids exerted definite degrees of protective action on the precipitation of gold suspension by sodium chloride. Lange applied the test to the fluid protein and found that normal fluid when diluted with a 0.4% sodium chloride solution does not affect the solution of colloidal gold, whilst in disease of the central nervous system characteristic changes are produced.

All cerebrospinal fluids precipitate colloidal gold, provided that the gold solution is sufficiently sensitive, but, generally speaking, the precipitating substance is contained to a small degree in normal fluid, to a greater degree

in tabetic cases, and to a still greater degree in paretic cases.—*Rep. Med. Res. Com.*, 1919-20.

Technique. Colloidal gold solution is red. Numbers are given to the colours formed on mixing the specimens with the gold; red=0, red-blue=1, violet=2, blue=3, bluish-white=4, and colourless=5. Ten dilutions are made, varying from 1/10 to 1/5120. Results are given from left to right. In *general paralysis* a typical reading would be 555554210 (the "paretic curve"). In *tuberculous meningitis* the figures may be 2221110000. In cerebrospinal syphilis 1223320000 is fairly typical.—A. Douglas Bigland, *Lancet*, ii/1920, 587.

Application of the test in disseminated sclerosis (during treatment with neoarsphenamine). The usual procedure of dilutions 1:10, 1:20, 1:40 of fluid in 0.4% sodium chloride was adopted, and 2.5 ml. of colloidal gold was added to each tube. The colour changes were noted in 1 hour and in 24 hours. The criteria of the suitability of colloidal gold for testing cerebrospinal fluid are (1) It must give a paretic curve with fluid from a case of general paralysis (2) Show no change with normal fluid (3) 5 ml. should be completely precipitated in 1 hour by 1.7 ml. of a 1% sodium chloride solution (4) It should be neutral to 1% alizarin red in 5% alcohol.—D. K. Adams, *Lancet*, i/1921, 420.

Cases of disseminated sclerosis give a positive curve in about 30% of the number of fluids tested.

In 20 cases of functional nervous disease the cerebrospinal fluid gave negative results. Apparently not specific, but of value to indicate first definite sign of involvement of the central nervous system in organic disease.—D. K. Adams, *Brit. med. J.*, ii/1921, 842.

The reaction is of value for differentiating one pathological condition from another, rather than as was first expected for making a quantitative determination of the protein.—*Physiology and Pathology of Cerebrospinal Fluid*, W. Boyd, 1920.

Preparation of the Gold Solution for the Reaction.

A number of slightly varied formulæ are available. To 100 ml. of triple-distilled water add 1 ml. of 1% solution of gold and sodium chloride ($\text{AuCl}_3, \text{NaCl}$). Bring to the boil and add 10 drops of 1% formalin. Remove partially from the flame and add 16 drops of 2% potassium carbonate solution and then at intervals of 15 seconds one or two more drops; 8 usually suffice. The colour should be a "smart blush," changing to old rose as it cools, with fluorescence. 5 ml. will be rapidly decolorised by 1.7 ml. of 1% sodium chloride, and it will give luetic and paretic curves with appropriate positives, and negative results with known negatives. Should not be used quite fresh but on the other hand it may not keep more than a week.—T. Grey, *Brit. med. J.*, ii/1922, 1120; i/1923, 88.

Gettler and Jackson's method.—*Yearb. Pharm.*, 1922, 38.

A simplified method: One ml. of 1% gold chloride and 1 ml. of 2% potassium carbonate are added to 100 ml. of water. This is heated and as it begins to boil 1 ml. of 0.5% glucose is added, and the boiling continued. Fluid turns violet in 1 minute, and then purple, when it is removed for use.—*Yearb. Pharm.*, 1922, 38.

Benzoin Reaction for Syphilitic Disease of the Central Nervous System.

One gramme of freshly powdered sumatra resin dissolved in 10 ml. of absolute alcohol; shake well and leave for 48 hours. Decant and add 0.3 ml. of the clear fluid to 20 ml. of *twice* distilled water at 35°. For each fluid to be examined, a series of 6 or 12 test-tubes is put up. Into the first tube 0.25 ml. of sodium chloride solution (0.01%) is placed, and into the remaining tubes 1 ml. of saline. 0.75 ml. of cerebrospinal fluid is measured into the first tube, and 1 ml. into the second tube; 1 ml. from the second tube is put into the third tube and mixed; 1 ml. from tube 3 is put into tube 4, etc., until the penultimate tube is reached, when, after mixing, 1 ml. is discarded; the last tube, containing only saline, acts as control. To each tube, including control, add 1 ml. of the gum benzoin suspension and mix; leave for 12 hours. In reading, three degrees of precipitation are recognised, 0, 1, and 2. In the first no change occurs; the second shows some precipitation, but fluid remains opaque; the third shows complete precipitation with clear supernatant fluid. "Negative" or "normal" readings, either no change whatever in all tubes, or precipitation in tubes 7 to 12 inclusive. A "positive" reading is complete precipitation in all tubes, with sometimes a slight deviation in tubes 11, 10, or 9, and sometimes the first tube

remains opaque. Test nearly as sensitive as Wassermann to syphilis of the central nervous system. Positive result is not obtained with any disease other than syphilis of central nervous system.—J. A. Braxton Hicks, and J. Pearson *Brit. med. J.*, i/1924, 268.

Mastic Test (introduced by Emanuel) is on lines practically identical with the previous excepting that mastic is used instead of benzoin.

In positive cases complete precipitation of the mastic occurs in a given number of tubes, and results are read in the same way as in the colloidal gold test. When precipitation is complete the fluid becomes perfectly clear, and there is a heavy white deposit at the bottom of the tube.—*Physiology and Pathology of the Cerebrospinal Fluid*, William Boyd, 1920.

Experiments with cerebrospinal fluid.—J. E. R. McDonagh, *Lancet*, ii/1922, 991.

The benzoin and mastic tests are of approximately equal value, but the benzoin is simpler. In special cases, such as meningitis and multiple sclerosis the colloidal gold test is preferable.—*J. Amer. med. Ass.*, ii/1925, 1584.

A Colour Reaction in General Paresis.

To 1 ml. of cerebrospinal fluid add 0.3 ml. of acetic anhydride. Shake well and add drop by drop 0.8 ml. of conc. sulphuric acid. Lilac tint indicates positive reaction; a brown-yellow or red-yellow tint a negative. Lilac tint appears immediately after addition of sulphuric acid, usually remaining about 5 minutes. Positive in 97% of cases of general paresis, and negative with almost every other type of mental disorder, except certain cases of neurosyphilis (other than general paralysis of the insane).—J. S. Harris, *Brit. med. J.*, i/1926, 136.

Tryptophane Test. In the diagnosis of tuberculous meningitis examine the cerebrospinal fluid for tryptophane as follows: Mix 2 to 3 ml. of the fluid with 15 ml. to 18 ml. of *B.P.* hydrochloric acid and 1 to 2 drops of 2% solution of formalin. In 5 minutes add slowly down the side of the tube 25 to 30 drops of a 0.06% solution of sodium nitrite. A positive reaction is shown by a violet ring being formed at the point of contact.—*Practitioner*, ii/1927, 63.

FÆCES

Examination of fæces is undertaken to determine the state of the various digestive functions, and is thus of assistance in the treatment of gastric and intestinal disease.

A trial diet is necessary. Ordinary meals are taken during 48 hours as follows: to include (1) milk undiluted or mixed with coffee; (2) eggs; (3) animal food, such as fish, poultry, veal, beef, etc.; (4) farinaceous foods—bread, potatoes, rice; (5) the various green vegetables and roots; (6) stewed fruit; (7) butter and various fats of meat.

The fæces are collected in a glass vessel—this permits macroscopic examination (*in constipation*, etc.).

Colour. The colour of normal stools varies considerably with the diet. A diet consisting chiefly of milk and carbohydrates will give pale yellow stools. A diet rich in meat will give dark brown stools. Black stools may be due to ingested drugs such as iron or bismuth, or to excessive bleeding, resulting in the tarry stool due to altered blood (melæna). Green stools of infants are usually due to bilirubin which owing to the rapid passage of the diarrhoeic stool has escaped conversion into stercobilin. Stools of very young infants contain bilirubin and these on exposure to air may turn green by oxidation of the bilirubin to biliverdin. The normal pigment of a stool is stercobilin and in adults bilirubin is abnormal.

Test for Bilirubin. To a smear of fæces on a white tile add two drops of fuming nitric acid. A blue or green colour denotes the presence of bilirubin.

Stercobilin (Urobilin). This is present in all normal stools, but is absent or deficient where there is any obstruction to the passage of bile into the intestine.

Test for Stercobilin. Make a thick emulsion of the stool with amyl alcohol and allow it to stand for 12 hours. Decant the supernatant fluid and after adding two drops of tincture of iodine mix with an equal volume of saturated zinc acetate in alcohol, and filter. The filtrate will be yellow or pinkish-yellow by transmitted light but will show a marked green fluorescence by reflected light if stercobilin is present.

Fats. The fat content of normal fæces on an average diet is:—

Neutral fat: 6% to 7%.

Free fatty acids: 7% to 8%.

Fat as soaps: 8% to 10%.

All calculated on the dried stool.

Neutral fat is increased in pancreatic deficiency. Free fatty acids and acid soaps (split fat) are increased in biliary deficiency, intestinal hurry and abnormal conditions of the intestinal mucous membrane preventing absorption.

Fat, Estimation of. Fat may be estimated by extracting 1 g. of dried stool in a Soxhlet's apparatus with ether. The ether extract is evaporated, dried and weighed. This weight is neutral fat and free fatty acid. The dried fats are re-dissolved in a little ether and after dilution with alcohol the free fatty acid is titrated with N/10 alcoholic KOH, phenolphthalein being used as indicator and each ml. of KOH being taken as equivalent to 0.0268 g. of fatty acid. The residue left after the first ether extraction is transferred to an evaporating basin and 10 ml. of 10% HCl in alcohol added (concentrated HCl 10, alcohol 100). This is placed on a water-bath and when reduced to about 5 ml. mixed with sufficient plaster of paris to make a paste. This is then carefully dried on the water-bath and the resulting powder replaced in the Soxhlet thimble and extracted with ether. The ether extract evaporated and weighed gives the amount of fat present in the form of soaps. Care must be taken not to confuse liquid paraffin and its numerous preparations with undigested fat.

An improved method for the determination of fat in fæces.—E. C. Wood and T. W. Simpson, *Analyst*, 1934, 817.

Protein. The only microscopic evidence of undigested protein in the stool is the presence of undigested muscle fibres. Many such fibres suggest pancreatic deficiency or possibly rapid passage through the small intestine.

Carbohydrate. Occasionally starch escapes digestion and appears in the stool. This may be recognised microscopically after the addition of a little iodine.

Fermentation. Set aside a portion in a fermenting flask. Distinct gas evolution in 12 hours shows that starch digestion has not been satisfactory. The fæces in this case are distinctly acid—catarrhal affections of the small intestine. Gas evolution after 24 hours or later shows that the albuminous substances are being split up by the increased alkalinity of the fæces. In the former case there is *intestinal fermentation dyspepsia*, and in the latter *intestinal decomposition dyspepsia*.

Vibrios. A new method of isolating and cultivating from fæces, especially suited for detection of vibrio-carriers in field work. Place 250 ml. of sterilised tank water in an enamel bowl with 1% of common salt; add 1 ml. of 1% sterile peptone solution immediately before inoculating medium with fæces. For collection and conveyance of stools large test-tubes (6 × 1 in.) are used containing 10 to 15 ml. of 1% salt solution. On arrival at the laboratory, or after 2 to 6 hours at room temperature, 6 large loopfuls of the surface liquids in the tubes are inseminated. Test surface layer of bowls daily—in positive cases, vibrios as a rule appear in 2 or 3 days, and when abundant persist in bowls for 2 to 4 weeks.—J. W. Tomb and G. C. Maitra, *Indian med. Gaz.*, 1926, 56.

Blood. Occult blood in stools may be recognised by:

Benzidine Test

The patient should have been on a meat-free and green-vegetable-free diet for at least 3 days. Superficial bleeding from the anus must be excluded. Bleeding from gums or nose should be looked for.

A small fragment of stool is mixed with about 5 ml. of water in a test-tube and boiled on a water-bath for 5 minutes. After cooling, it is added to about 5 ml. of saturated solution of benzidine in glacial acetic acid to which 10 drops of 10 vol. hydrogen peroxide have been added. On shaking, a blue colour shows the presence of blood. The test is extremely sensitive, and faint or doubtful reactions should be ignored.

Meyer's Phenolphthalin Reagent. Phenolphthalein, 2 g., potassium hydroxide 20 g., water 100 ml. Dissolve and add zinc 10 g., and boil. Filter while hot (and decolorised). Keep in the dark with a little zinc at the bottom.

In using, a small piece of fæces is taken from the middle of the stool after a milk diet and made into a fine suspension by adding water. Fill a test-tube about one-third full with this. Add one-third of its volume of glacial acetic acid, mix, boil and cool under tap. Add 5 ml. of ether, mix well and set aside. Pipette off and add 1 ml. of the reagent and a few drops of hydrogen peroxide. If blood is present an *immediate* deep red colour spreads down the tube.

Blood in water gives a positive reaction 1 in 500,000. A slightly modified form of the test employed. Copper, even in traces, interferes with the test.—*J. chem. Soc. Abstr.*, ii/1922, 724.

Amidopyrine (Pyramidon) Test.—Take 5 ml. of a boiled and cooled stool emulsion in water. Add 3 to 4 drops of acetic acid and then 2 ml. of 5% amidopyrine in alcohol so that a layer of the latter is present on the surface. Drop in 5 to 6 drops of 10 vol. hydrogen peroxide. A mauve colour spreading up into the amidopyrine layer will show the presence of blood. This test is a good one although not nearly so sensitive as the benzidine test.

Thymolphthalein Test.

Dissolve thymolphthalein 1 in water 100 and add potassium hydroxide 25 and zinc powder 10. Boil until colourless, filter hot and make up to original volume. Keep zinc filings in the solution to prevent oxidation.

To use the test, rub down a small portion of the fæces (e.g. the size of a bean) with 5 to 10 ml. of alcohol and 20 drops of glacial acetic acid. 25 to 30 drops of the extract are filtered off and 20 drops of the reagent mixed with 15 drops of hydrogen peroxide added. On shaking, a greyish-blue opaque ppt. forms, turning blue on standing if blood is present.—*Yearb. Pharm.*, 1919, 46.

Microscopic Examination. The presence of *connective tissue and elastic fibres* indicates a defect in acidity of the gastric juice. Defective dissociation of connective tissue and coagulable proteins points to a primary gastric affection known as *achylia gastrica* (*Hayem's hypopepsia*). Appearance of elastic fibres, if not associated with connective tissue and coagulated protein, must be regarded as a sign of good gastric, but defective intestinal digestion. Considerable amount of undigested muscle fibre with well-marked contour may indicate bad intestinal digestion of meat.

Mucus. Stain smear with 1% sodium alizarine sulphonate. Normal mucus appears as small, faintly yellow flakes and scales. It is possible to determine the section of the intestine from which mucus is derived by the tint of this colour—the further the distance to the anus the mucus has to travel the lighter the colour.

Detection of trypsin in the fæces to assist diagnosis of pancreatic disease. Rub up a small quantity with glycerin, place on a serum plate and incubate at 55° to 60° for 24 hours; note occurrence of depression in the medium. The reaction is not due to pepsin. The amount of ferment was found to be distinctly greater in loose stools or diarrhœa, indicating that probably owing to the increased peristalsis the reabsorption or destruction of ferment is hindered and an increased quantity voided.

THE FÆCES IN ALIMENTARY DISORDERS. For a consideration of the subject, control of diet, macro- and microscopic examination, etc., see R. Coope, *Lancet*, ii/1921, 9; also Chalmers Watson, *ibid.*, 153; reply, *ibid.*, 362. The bacteria present in the fæces are not for the most part dead, as commonly taught. Saccharose milk agar—a new medium apparently selective for intestinal bacteria.—D. Chalmers Watson, *Lancet*, ii/1922, 127.

PLEURAL AND PERITONEAL FLUIDS

Physical Characters.

Note whether blood-stained or not. (Caution: A small amount of blood may get into the fluid in the process of exploring).

Observe whether transparent or otherwise.

Test for fat.

Note the consistence, specific gravity, odour, amount and nature of deposit.

Chemical Investigation will give:—

(1) Reaction, (2) Presence of serum albumin and serum globulin, (3) Presence of mucin or nucleo-albumin by addition of acetic acid.

Microscopic Examination of Sediment. For blood, epithelial cells, cancer cells, Foulis' cells (these are met with in fluids from malignant ovarian cysts or malignant peritonitis following such cysts), hooklets, crystals, actinomycosis nodules, *Amœba dysenteriae*.

General Characters. It is difficult to tell a dropsical from an inflammatory fluid. It appears that the amount of proteins in an effusion depends much more upon site than upon cause. Pleural fluids contain the highest percentage of proteins, peritoneal fluids rather less and subcutaneous fluids very little. The fluid in cardiac dropsy is more highly albuminous than in dropsy of renal origin. Diagnostically all one can say is that a fluid with sp. gr. more than 1·018 containing more than 4% of albumin is almost certainly inflammatory while one with sp. gr. less than 1·015 and an albumin percentage less than $2\frac{1}{2}\%$ is certainly dropsical. Fluid obtained by lumbar puncture in cases of cerebral tumour has a sp. gr. 1·006 and a protein content of 0·5% in chronic cases up to 1 or 2% in acute stages.—For further details see R. Hutchison and H. Rainy, *Clinical Methods*.

STOMACH CONTENTS

In a healthy subject food commences to pass the pylorus in from fifteen minutes to half an hour after ingestion, the time varying with the character of the food (e.g., carbohydrates leave the stomach before proteins), and the stomach is empty in five hours. The passage through the small intestine takes about three and a half to five hours, about one inch a minute, so that there is food in the cæcum before the whole meal has left the stomach.

Test Meals.

Ewald Test Meal. This consists of 2 oz. of toast without butter and half a pint of tea without milk. The meal is removed one hour after its ingestion by means of an œsophageal tube either by a syringe or a Senoran's bottle. This type of test meal has been replaced by the Fractional Test Meal.

Fractional Test Meal. The patient swallows a Ryle's tube and then drinks a meal of weak oatmeal gruel. This is made by adding 2 tablespoonfuls of oatmeal to a quart of water, boiling gently until the volume is reduced to a pint and then straining through muslin. Before taking the gruel the stomach is emptied by gentle aspiration with a syringe and the fluid examined as a sample of resting juice. If there is any question of delay it is an advantage to give the patient a charcoal biscuit the night before the test. Any charcoal in the morning resting juice will be definite evidence of delayed emptying of the stomach. Samples of the gastric contents are withdrawn at half hourly intervals and each analysed for its HCl content, total acidity and total chloride content. A note is made of the appearance of any blood or bile in any specimen. The rate of emptying is judged by the disappearance of starch from any sample. It is usual to continue the examination up to two hours.

Examination of Sample of Gastric Fluid. The presence of blood, charcoal and bile can be detected by the naked eye. Chemical tests for blood are unsatisfactory as it is common to get positive reactions, probably due to traces of blood produced by trauma. Before beginning the chemical examination the specimen should be filtered.

Free Hydrochloric Acid. This can be determined by Gunzburg's test. Mix six drops of 10% phloroglucin in alcohol with half the quantity of 10% vanillin in alcohol. Place this in an evaporating basin and add two or three drops of the filtered specimen. Evaporate gently on a water-bath. If free hydrochloric acid is present the residue will assume a deep cherry colour.

Thymol Blue. Add a few drops of 0.1% thymol blue to 10 ml. of the test meal filtrate. A red colour shows the presence of free hydrochloric acid. The amount present can be determined by titrating this solution with N/10 NaOH until the solution becomes yellow at pH 2. Each ml. of N/10 NaOH is equivalent to 0.00365 g. of HCl.

Total Acidity. This can be estimated in the same solution by continuing the titration until the indicator becomes blue. The reading of the titration from the beginning until the blue end-point, pH 8.8, is reached is a measure of the total acidity. The result can be expressed in terms of hydrochloric acid or as the number of ml. of N/10 NaOH equivalent to 100 ml. of test meal.

Estimation of Total Chlorides. To the same 10 ml. of the filtrate add 15 ml. of N/10 AgNO₃ and 3 ml. of conc. HNO₃. Heat on a boiling water-bath and add saturated solution of potassium permanganate until the brown colour goes with difficulty. This will indicate the almost complete destruction of organic matter. Cool and add a few drops of 10% ferric alum as indicator. Titrate the excess of silver nitrate with N/10 KCNS. The chloride may be expressed in terms of HCl or again as number of ml. of N/10 NaOH equivalent to 100 ml. of test meal.

Alcohol Meal. This is of value in cases of suspected pernicious anæmia where the important point is the presence or absence of free hydrochloric acid. 50 ml. of 7% alcohol are given and samples of the contents of the stomach aspirated in the usual way up to an hour. If at the end of this time no free HCl has appeared a hypodermic injection of 0.1 mg. of histamine is given and the half-hourly collection of specimens continued. If at the end of 2 hours there is no free acid it can definitely be taken as a condition of achlorhydria.

Definition of terms. The following classifications are suggested by Harrison:

	Ewald Test Meal	Fractional Test Meal
FREE HCl		
Achlorhydria	Absent	Absent throughout
Hypochlorhydria	1 to 19 ml. of N/10%	Never above 10 ml. of N/10%
Isochlorhydria (normal free HCl)	20 to 60 ml. of N/10%	Ranges between 11 and 60 ml. of N/10%
Hyperchlorhydria	Over 60 ml. of N/10%	One or more points above 60 ml. of N/10%
ACIDITY		
Anacidity	Absent	Absent throughout
Hypoacidity	1 to 29 ml. of N/10%	Never above 20 ml. N/10%
Isoacidity (normal acidity)	30 to 70 ml. of N/10%	21 to 70 ml. of N/10%
Hyperacidity	Over 70 ml. of N/10%	Over 70 ml. of N/10% at one or more points.

Achylia. Absence of free HCl and of pepsin with low chlorides, i.e., absence of gastric secretion.

Gastric function in health and disease.—J. A. Ryle, *Lancet*, i/1925, 583, 641; 697, 754.

The technique and clinical interpretation of the fractional method of gastric analysis.—L. M. Morris, *J. Roy. Nav. Med. Service*, 1926, 89.

The following are abstracts from the works of Willcox, Herschell, Martin and others:—

Chemical Examination of the gastric contents after a test meal containing little protein and nitrogenous bases.—Willcox.

The hydrochloric acid in this case will be present as far as possible in the free condition (which is the point of importance in diagnosis of gastric ulcer).

I. Total Acidity (Normally = 0.15% HCl). Determine whether there is active hydrochloric acid or a mixture of this and organic acid. Usually in chronic gastritis acidity is low. In gastric ulcer it is high. In carcinoma it is usually low. (A normal acidity does not exclude gastric carcinoma.)

It is increased in simple hyperchlorhydria, peptic ulcer, cholelithiasis, appendicitis, and colitis.—*Lancet*, i/1913, 462.

Without doubt both total acidity and free hydrochloric acid are raised in a considerable proportion of ulcer cases. Duodenal cases show on an average a larger and more constant increase of acidity than the ulcers on the gastric side.—*Brit. med. J.*, ii/1912, 940, *et seq.*

Litmus Paper is affected by hydrochloric, lactic and butyric acids.

Congo Red Paper. The colour caused by organic acids will disappear on warming over a spirit lamp whilst that due to hydrochloric acid remains.

II. Hydrochloric Acid. This, according to Willcox, is either (a) *free*, (b) *combined* with protein and organic bases (i.e., *physiologically active*), or (c) *inorganically* combined (i.e., *physiologically inactive*). Normally free HCl is 0.1%.

(a) **Phloroglucin Test for Free Hydrochloric Acid** (Gunzburg):—

Phloroglucin 2 g., vanillin 1 g., alcohol 90% 30 g. A rose-red colour, formed on warming a few drops with an equal amount of the specimen in a porcelain dish, indicates presence of the acid. May also be best kept in powder form—2 parts of phloroglucin and 1 part of vanillin. As much as will lie on the point of a penknife, added to a few drops of alcohol, forms a perfectly reliable solution. This is the most trustworthy.

This test is positive with free mineral acids and may be relied on to show the absence of free hydrochloric acid.—*Lancet*, ii/1912, 1104.

Resorcin will do instead of phloroglucin—a few crystals of this and of vanillin dissolved in a drop of the test meal and evaporated to dryness give a clear result—slightly more purple than with phloroglucin. The result is positive with very dilute hydrochloric acid in protein solution, and negative with combined hydrochloric acid and with lactic acid.—P. N. Panton, *Lancet*, ii/1918, 125.

Response to **dimethylaminoazobenzene** may be given by organic acids. In gastric ulcer and hyperchlorhydria free hydrochloric acid is always present; in carcinoma it is scarcely ever present.

Boas' Test for Free Hydrochloric Acid. Resorcin 5, cane sugar 3, alcohol 100. This test is used exactly as Gunzburg's test, the same red colour being produced, but Boas' solution requires heating more carefully, as it chars more readily and the colour is not permanent.

(b) **Physiologically Active Hydrochloric Acid**, i.e., free and combined with protein and organic bases (normally about 0.15%).

Willcox's Modified Volhard Method. Two equal quantities (20 ml.) of gastric contents are taken and in one the total chlorides is estimated by adding excess of N/10 silver nitrate and back titrating with ammonium sulphocyanide. From the other quantity free HCl and the acid combined with organic nitrogen compounds are removed by evaporation and gentle ignition, the remaining inorganic chlorides being then determined as before. Difference gives *active* HCl. In gastric ulcer and hyperchlorhydria the active HCl is equal to or nearly equal to the total acidity, and is usually over 0.15%. In gastric carcinoma the

active HCl, as found by Willcox, is nearly always much reduced—always under 0.1%. In chronic gastritis the active HCl is often below normal.

Differential Estimation of Physiologically Combined and the Free Acid. The fluid is titrated with alkali in presence of dimethylaminoazobenzene as indicator, the result being the physiologically combined + free hydrochloric acid; then another portion is titrated with alizarin red (1% aqueous solution) as indicator, which gives free hydrochloric acid only. The amount of alkali required in the first titration minus the amount required for the second titration is the amount required by the *physiologically combined hydrochloric acid*, i.e., hydrochloric acid combined with proteins and other weak bases, e.g.:

1st titration showed 0.2% calculated as hydrochloric acid.

2nd titration showed 0.15% free hydrochloric acid.

$0.2\% - 0.15\% = 0.05\%$ physiologically combined hydrochloric acid.

Töpfer's Test. Solution *A*: 0.5% dimethylaminoazobenzene. Solution *B*: 1% alcoholic phenolphthalein.

Add one drop of Solution *A* and one drop of Solution *B* to 5 ml. of the filtered gastric juice. Titrate with N/10 NaOH until the red colour changes to yellow. This gives the content of free HCl on multiplying the number of ml. of N/10 NaOH by 20 and then by 0.00365.

On titrating the solution with the N/10 soda until a pink colour due to the presence of Solution *B* is produced, the quantity of N/10 soda used gives the total acidity.

Total chloride concentration and acidity of the gastric contents.—*Brit. chem. Abstr. A.*, 1928, 1153.

III. Organic Acid, Lactic Acid. According to Willcox, great importance should not be attached to presence or absence of this acid. Organic acids in considerable amount are present in carcinoma of the stomach and where much fermentation is going on.

Uffelmann's Test for Lactic Acid (not entirely satisfactory). Ferric chloride solution 1 drop, phenol 0.4 g., water to 50 ml. (Delicacy limit 1 : 10,000—the violet colour changes to yellow).

An approximate estimation may be conducted as follows:—

Distil 30 ml. from 40 ml. of the filtered stomach contents the total acidity of which is known. The volatile acids pass over: the residue contains the lactic and hydrochloric acids. The acidity of the distillate (found by titration with N/10 soda, using phenolphthalein as indicator) deducted from the total acidity "A" (found by titrating 10 ml. of the filtered stomach contents in the same manner, the result being expressed in terms of hydrochloric acid) gives the amount of lactic and hydrochloric acids together. If the amount of HCl "H" (found in the same way as "A," but using dimethylaminoazobenzene as indicator) be deducted from this, the remainder is **Lactic Acid**.

Mucin. In gastric ulcer and hyperchlorhydria usually absent. In gastric carcinoma a definite precipitate occurs on adding 2% acetic acid. In simple gastritis often present in small amount.—Willcox. It is soluble in sodium hydroxide solution. Dried film is deeply stained reddish violet by thionin staining solution.

Mucus normally is stained faintly, but that met with in chronic gastritis deeply, with methyl green.

Ferment Activity. Determination of pepsin and pepsinogen present is of great importance. The method of Willcox is as follows:—

Action on milk by determination of the activity of the gastric juice by rennin contained (usually proportionate to pepsin) by using a series of tubes containing 5 ml. of milk, to which are added gradually increased quantities of the gastric juice, and the mixtures maintained at 40° for 30 minutes. About 0.2 ml. of normal gastric juice (of the adult) is required in this test.

In *gastric carcinoma* much more.

In *gastric ulcer* and hyperchlorhydria usually less (0.05 ml. or less).

In certain cases it may be necessary to estimate **renninogen**.

Rennin is tested for by adding a few drops of the filtered and neutralised stomach contents to two or three ml. of milk and maintaining the mixture at 98°F. for 15 minutes; resulting coagulation indicates presence.

For testing for **rennin zymogen**, a small quantity of calcium chloride is added prior to incubation. A pocket incubator may be used for these experiments.

Digestive activity of the stomach contents (i.e., amount of pepsin secreted) increases or diminishes with the amount of hydrochloric acid secreted by the mucous membrane. A number of cases of gastric carcinoma compared with cases of ulcer and functional disease showed that, on the whole, the greater proportion of cases evidenced a great diminution of acid secreted, as well as diminution of digestive power.—S. Martin, *Lancet*, i/1909, 398.

Nitrogen Factor. The phenolphthalein and dimethylaminoazobenzene readings of acidity are employed to give what is termed the Nitrogen Factor. In an active stomach “*Phenol*” minus “*Dimethyl*” reading is a constant under normal test nitrogen meals, etc. A certain multiple of this constant—the Nitrogen Factor—is normally about 2·4. A rise above this indicates stasis or impairment of the digestive process. Table of 19 cases presenting appendicular disturbance.—C. Singer, *Lancet*, ii/1912, 1711.

Test for the products of **Starch Digestion.** The presence of erythrodextrin in any quantity (giving a brown colour with Lugol’s Solution) one hour after a test breakfast will point to hypochlorhydria.

Gunzburg’s Capsule, for testing digestive power, consists of $\frac{5}{16}$ inch of thin rubber tubing, $\frac{1}{8}$ inch in diameter, containing $1\frac{1}{2}$ grains of potassium iodide plugged with pledgets of fibrin at each end.

Fermentation is examined by means of an ordinary Doremus Ureometer.

Estimation of the **digestive power** of the gastric juice is effected with hard boiled egg by examining for peptone after two hours or so at 40°.

Peptic Index ascertained by means of **Edestin**, a substance made from hempseed, purified by recrystallisation from warm salt solution. It is soluble 1 in 60 of 0·2% hydrochloric acid, 1 in 25 of 0·5% sodium hydroxide, about 1 in 460 of 4% sodium chloride (Fuld’s method, see S. W. Cole’s *Practical Physiological Chemistry*).

NUTRITION

(For details concerning various foods and food products see the section in Volume I on Nutrimenta.)

For the maintenance of health, and for satisfactory growth the food intake, in addition to oxygen and water, must consist of the following factors:—

- (1) PROTEIN from plants and animals.
- (2) FATS.
- (3) CARBOHYDRATES (starches, sugars, and cellulose).
- (4) Certain INORGANIC SALTS.
- (5) All the VITAMINS: the existence of at least six has been recognised; there are probably many more.

Proteins constitute most of the nitrogenous elements of animal and vegetable tissues. On digestion, they are converted in the stomach, by the action of the enzyme pepsin, to proteoses and peptones; and then, on further hydrolysis in the intestine by trypsin and erepsin, to amino-acids. Some of the amino-acids are absolutely essential for the building up of tissue. It is stated that kidney, liver and milk proteins are of unusual value. On the other hand, some, for example, gelatin and zein of maize, do not yield all the important amino-acids, and therefore are of less value than many other proteins.

The amino-acids not required by the system are broken up by the liver cells, the nitrogen being excreted as urea, creatinine, uric acid, etc., and the balance of the molecule converted into glycogen or neutral fats.

Fats are converted into glycerol and fatty acids by the enzyme lipase secreted by the pancreas, the action being facilitated in the intestine by the emulsifying power of the bile. The products of digestion are absorbed by the cells covering the villi in the small intestine and are passed on as neutral fats by the lacteal system to the blood. They are then stored in the tissues or oxidised to produce heat and energy.

Carbohydrates may be classified as

- (1) MONOSACCHARIDES of the formula $C_6H_{12}O_6$ (glucose, galactose, fructose, etc.).
- (2) DISACCHARIDES ($C_{12}H_{22}O_{11}$) include saccharose, maltose, lactose.
- (3) POLYSACCHARIDES include starch, cellulose, glycogen and dextrin.

During digestion the carbohydrates are hydrolysed by appropriate enzymes and are finally absorbed as glucose and lævulose. These are converted to glycogen by the action of insulin, and this starch is stored in the tissues to be gradually liberated when required, furnishing heat and energy by oxidation. If excess of carbohydrates is assimilated it is converted into neutral fats and stored as such.

Inorganic Salts. Complete deprivation results in the death of the individual within a month. The following elements, in addition to carbon, hydrogen, nitrogen and oxygen, enter into the composition of the tissues: calcium, potassium, sodium, magnesium, phosphorus, sulphur, iron, chlorine, and iodine. Traces of silicon and fluorine are present in the bones and teeth. Cereal foods and tubers are lacking in sodium, phosphorus, calcium, and chlorine. Meat is rich in phosphorus. Leafy green vegetables, most fruits, and milk, supply salts, but the latter is deficient in iron. Traces of copper are necessary for the formation of hæmoglobin, although copper itself does not constitute part of the hæmoglobin molecule.

The endocrine secretions influence metabolic activity and therefore the vital processes of the organism.

Errors of diet, and especially the ingestion of excessive quantities of carbohydrates, with the probability of accompanying gastric fermentation, are thought to be predisposing factors in such diseases as pellagra, sprue, tuberculosis, nephritis, calculi, arteriosclerosis and diabetes.

Sucrose taken in large amount with a meal is especially prone to fermentation, with the production and absorption of irritating organic acids and toxic products. Abundance of carbohydrate also usually implies a deficiency in mineral salts and vitamins.

(i) **Proteins. Biuret Reaction.** This reaction is one of several general reactions for proteins.

To obtain good results with the test in the recognition of protein, the test solutions of copper sulphate and sodium hydroxide are best of following strengths:—sodium hydroxide 1 g. in 10 ml., and copper sulphate 0.5 g. in 100 ml. water. Egg albumin, proteoses and peptones give a pink colour: other proteins give a violet colour. Urea also gives the reaction.

Amino-acids. On hydrolysis, proteins are broken down into metaproteins, proteoses, peptones and ultimately to amino-acids. The number of different amino-acids varies in different proteins. The proportions in which they are combined in different proteins varies also. Eighteen or nineteen different amino-acids have been isolated. Some of them are absolutely essential for nutrition, others apparently are not. A protein which contains all the necessary amino-acids combined in the right proportion is said to be of high biological value. Casein and lactalbumin are probably the most valuable proteins available but there can be no doubt that it is safer to take a mixture of proteins than to try to take only one. Gelatin is a poor protein as it contains no cystine or tryptophane.

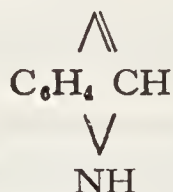
It is still not known whether pellagra is due to the poor quality of the protein eaten or to a lack of one of the B vitamins, possibly B₂, or to some toxic substance in the seed of maize.

No protein has yet been synthesised, though Fischer has built up polypeptides containing as many as 18 molecules of amino-acids linked together, but even this is simple compared with a protein.

The molecular weight of one of these polypeptides is about 1050, whereas the molecular weight of the protein ox-hæmoglobin is about 16,320.

Amino-acids contain the amino (NH_2) group. They are both basic and acidic, e.g.:—

Glycocoll $\text{CH}_2(\text{NH}_2)\text{COOH}$. (Amino-acetic acid.)
 Sarkosine $\text{CH}_2(\text{NH}\cdot\text{CH}_3)\text{COOH}$. (Methyl-glycocoll.)
 Alanine $\text{CH}_3\cdot\text{CH}(\text{NH}_2)\text{COOH}$. (α -Amino-propionic acid.)
 Leucine $(\text{CH}_3)_2\text{CH}\cdot\text{CH}_2\cdot\text{CH}(\text{NH}_2)\text{COOH}$. (α -Amino-caproic acid.)
 Aspartic Acid $\text{HOOC}\cdot\text{CH}_2\cdot\text{CH}(\text{NH}_2)\text{COOH}$. (Amino-succinic acid.)
 Glutaminic Acid $\text{HOOC}\cdot(\text{CH}_2)_2\text{CH}(\text{NH}_2)\text{COOH}$. (α -Amino-glutaric acid.)
 Tyrosine $\text{HO}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{CH}(\text{NH}_2)\text{COOH}$. (β -parahydroxyphenyl- α -amino-propionic acid.)
 Tryptophane $\text{C}\cdot\text{CH}_2\cdot\text{CH}(\text{NH}_2)\cdot\text{COOH}$ (β -indole- α -aminopropionic acid).



Amino-acid fractions of the protein molecule are occasional constituents of the excreta, e.g., leucine, tyrosine, cystine, in which last the sulphur of proteins resides. From others the equally familiar excretory products, or products of putrefaction, are derived—such as indole from tryptophane, cadaverine from lysine, and putrescine from arginine.

The amount of protein food needed for the actual physiological want of the body would be not more than half that ordinarily consumed by the average man if all the protein eaten were of high biological value. A diet of low protein content is generally recommended for a healthy man and for those suffering from arteriosclerosis.

Excessive protein feeding as such is not harmful to the kidneys—the damage done to them being due to lack of vitamins in the diet.—Work at St. Thomas's Hospital, *Pharm. J.*, i/1926, 293.

(ii) **Fats.** This group comprises the glycerides of a large variety of fatty acids, e.g., oleic, palmitic, stearic, etc. Mention may also be made of lecithin, which is an important constituent of eggs and various animal tissues, and the important group of substances known as sterols, one of which, ergosterol, is the precursor of vitamin D. This sterol is not apparently synthesised in the body and must be supplied in the food. The type of fatty acid present in the ingested fat is important; thus, fats such as linseed oil, containing highly unsaturated fatty acids have greater inhibitory effect on gastric secretion than fats like olive oil which contain more saturated fatty acids.

In carbohydrate starvation, oxidation of fat may be incomplete, and intermediate products, β -hydroxybutyric acid, acetoacetic acid, and acetone, will pass into the blood and urine. Two ounces is usually considered the average daily allowance of fat for an adult.—S. J. Cowell, *Lancet*, i/1929, 996.

(iii) **Carbohydrates.** Importance of removing carbohydrate matter from the teeth. Many organisms in the mouth ferment carbohydrates, producing chiefly lactic acid. Monosaccharides are the most readily fermented. Disaccharides require to be first inverted to monosaccharides by an enzyme formed by certain of the mouth organisms before lactic acid can be produced. Starches require a double inversion—the first stage brought about by ptyalin or organisms before fermentation to an acid can occur. 1 mol. $\text{C}_6\text{H}_{12}\text{O}_6$ (glucose) produces 2 mols. of lactic

acid; 1 mol. of the disaccharide cane sugar $C_{12}H_{22}O_{11} + 1$ mol. H_2O gives 1 mol. each of dextrose and lævulose, with ultimate formation of lactic acid; and the polysaccharide $(C_6H_{10}O_5)_n$ (starch) + H_2O gives $(C_6H_{10}O_5)_x$ (dextrin) + $C_{12}H_{22}O_{11}$ (maltose), which maltose is converted into 2 mols. dextrose, and ultimately to lactic acid. The lactic acid dissolves the lime salts of the enamel and a cavity is originated at the point of action.

This theory of the cause of decay of teeth is still held by some. Others accept the work of May Mellanby which shows the influence of diet on the structure of teeth. Undoubtedly, sufficient amounts of vitamin D in the diet (as cod-liver oil or as solution of irradiated ergosterol) result in the formation of stronger milk teeth, and the retardation of the rate of progress of caries in teeth already erupted. For references, see vitamin D.

The carbohydrate content of food, by R. A. McCance and R. D. Lawrence, *Spec. Rep. Ser. med. Res. Coun., Lond., No. 135, 1929.*

(iv) **Inorganic Salts.** **Iron**, in the presence of copper, enters into the elaboration of hæmoglobin.

The Use of Iron and Copper in Nutritional Anæmia.

A large proportion of artificially-fed infants suffer from nutritional anæmia which can be cured by treatment with iron.—H. M. Mackay, *Spec. Rep. Ser. med. Res. Coun., Lond., No. 157, 1931.*

Cases of nutritional anæmia in children responded to treatment with iron and copper more quickly than to treatment with iron alone.—M. S. Lewis, *J. Amer. med. Ass., i/1931, 1135.*

Inorganic iron (ferric chloride) is more beneficial in treatment of nutritional anæmia than organic iron (hæmatin compounds) though the latter is improved by the addition of copper.—C. A. Elvehjem, *J. Amer. med. Ass., i/1932, 1047.*

An analysis of the anæmia of pregnancy. This form of anæmia is independent of the diet given since it occurred on a diet containing everything known to prevent nutritional anæmia.—E. C. van Donk, H. Feldman and H. Steenbock, *Amer. J. Physiol., 1934, 107, 616.*

The nutritional anæmias of man and animals.—L. S. P. Davidson and I. Leitch, *Nutr. Abstr. Rev., 1933-4, 901.* A review.

Iron therapy in anæmia.—A. J. Clark, *Pharm. J., i/1932, 490, 511; ii/1932, 2, 22.*

See also Waddell, Hart, Steenbock and Elvehjem, *J. biol. Chem., 1928, 77, 797.*

Iodine enters into the elaboration of thyroxine. For references to iodine in nutrition, etc., see references to iodine in natural waters, p. 475.

Alkalis and **alkaline earths**, with **chlorine** and **phosphorus**, control a constant osmotic pressure in the body.

Calcium must be continually supplied in large quantities, as it is excreted even in the absence of intake, symptoms of disease being thereby produced.

Fluorides present in drinking waters have recently been found to cause mottling of the enamel in teeth. For references see Notes on Water Analysis, p. 475.

CALORIE VALUES OF FOODS

The following figures (**Calories**) are usually given as the true worth to the body of the different nutritive constituents as sources of potential energy: protein 4, carbohydrates 4, fat 9 calories.

Proteins and carbohydrates seem to be oxidised quickly in the tissues, fats more slowly. Therefore, if a rapid output of energy is required, the *first* group will be more serviceable, whereas a slow production over a long time will be equally well met by fat.

Method of Applying the Calorie Standard. Multiply the percentage of protein and carbohydrate that the food contains by 4·1 and the percentage of fat by 9·3 to obtain the total calories yielded by 100 parts of the food in question.

A Calorie (i.e., a kilo calorie) is the amount of heat necessary to raise 1 litre of water 1° C. or 1 lb. of water 4° F.

STANDARD NUTRITIVE REQUIREMENTS

Cathcart and Murray Scale

	Calories	Man Value		Calories	Man Value
Adult woman	2500	0·83	Child 6 to 8	1800	0·60
Boy of 14 or over	3000	1·00	„ 3 to 6	1500	0·50
Girl of 14 „ „	2500	0·83	„ 2 to 3	1200	0·40
Child 12 to 14 „	2700	0·90	„ 1 to 2	900	0·30
„ 10 to 12	2400	0·80	„ 0 to 1	600	0·20
„ 8 to 10	2100	0·70			

The calorie needs of the adult male being taken in the above scale as 3000 great calories per day.—E. P. Cathcart and A. M. T. Murray, *Spec. Rep. Ser. med. Res. Coun., Lond., No. 151, 1931; Lancet, i/1933, 597.*

Report of B.M.A. Committee on Nutrition. Appointed April 12th, 1933. "To determine the minimum weekly expenditure on foodstuffs which must be incurred by families of varying size if health and working capacity are to be maintained, and to construct specimen diets."

The committee gave the estimated cost of minimal diet for Stockton-on-Tees (which has the cheapest food-markets in the country) from 5s. per week for an adult male to 2s. 6d. per week for a child between 1 year and 2 years of age (the corresponding costs on the B.M.A. scale being 5s. 11d. and 2s. 8d.). The coefficient of cost of children's diet between 1 and 10, expressed in terms of an adult male's minimum diet (=1) is above the usually accepted man-value for calories, namely 0·47, as compared with the Cathcart and Murray scale of 0·30 for a child between 1 and 2, the reason being the child's greater need for food such as milk. The main assumptions on which the committee's estimates are based are (1) 3,400 great calories are needed to keep an adult male in health and working capacity, (2) the calorie needs of women and children are best expressed by the Cathcart and Murray scale, though possibly this is too low for children, (3) 50 g. first-class protein (from animal sources) are needed daily for adult males, (4) the diet should contain 100 g. protein, 100 g. fat, 500 g. carbohydrate, (5) children between 1 and 5 need a pint of milk daily and between 5 and 10 half a pint.—*Brit. med. J. Supplement, Nov. 25th, 1933, also leading article, ibid.*

A conference between physiologists representing the **Nutrition Advisory Committee of the Ministry of Health** and the **Nutrition Committee of the B.M.A.** considered that a workable solution of the problem of physiologically desirable dietary standards for individuals could only be found in a sliding scale of caloric needs based on age, individual physique, occupation and habits, and adopted the following as a working basis:—

Man: heavy work . .	3400 to 4000	Child: 12 to 14 —	2800 to 3000
Man: moderate work	3000 to 3400	„ 10 to 12 —	2300 to 2800
Man: light work . .	2600 to 3000	„ 8 to 10 —	2000 to 2300
Woman: active work	2800 to 3000	„ 6 to 8 —	1700 to 2000
Woman: housewife	2600 to 2800	„ 3 to 6 —	1400 to 1700
Boy: 14 to 18 . .	3000 to 3400	„ 2 to 3 —	1100 to 1400
Girl: 14 to 18 . .	2800 to 3000	„ 1 to 2 —	900 to 1100

The conference stated that "such a sliding scale should not, however, be interpreted in too rigid a sense, for the unique nature of each individual's food requirements cannot be too strongly emphasised."—*Brit. med. J., i/1934, 900.*

The athletic schoolboy requires as much as 5000 calories.—J. A. Nixon, *Brit. med. J., i/1934, 3.*

Calorie Values (kilo calories) of a few common foods

Milk 0.70.	Coarse white bread 3.03.
Potatoes 0.98.	Fat beef 3.27.
Lean beef 0.98.	Peas 3.31.
Eggs 1.59.	Lentil flour 3.55.
Cheese 2.4.	Fat mutton 4.03.
Fine wheat bread 2.74.	Butter 8.60.
Wholemeal bread 2.78.	Bacon 8.86.

—Hutchinson's *Food and Principles of Dietetics*.

Apples, fresh, 0.53.	Cream 2.07.
Bananas, without skin, 0.80.	Dates, dried, 3.30.
Cabbage	Fish 1.10.
Cauliflower	Grapes 0.66.
Carrots	Margarine 7.50.
Onions	Rabbit 2.9.
Turnips	Rice, boiled, 0.93.
Chicken 1.40.	Tomatoes 0.17.

—U.C.H., 1926.

The above calorie values are calculated from the percentage composition and represent *the kilo calories yielded by complete combustion of 1 g. of each*.

The lack of fat is a serious matter when preserved meat is used. The proportion of fat to meat in fresh meat is about 1 to 4, but in corned beef this is reduced to 1 to 10. A good form of fat ration is cheese, but lard and suet are also suitable.

The added fat should be one containing the fat-soluble vitamins, e.g., butter, suet, or one of the vitaminised margarines. Lard is generally deficient in these factors. Since only a limited amount of fat can be digested, particularly by children, it is important that the fat which is eaten should contain vitamins A and D.

NUTRITION GENERALLY

A deficiency of available iron, and possibly also of copper, in the diet of infants, leads to susceptibility to infection—particularly colds, bronchitis, enteritis and otorrhœa with a tendency for these infections to become chronic. Iron and ammonium citrate should be given to infants as an addition to the diet, or dried milk preparations containing iron should be ordered.

Of the utmost importance that the diet of pregnant and nursing mothers and of infants and young children should include a sufficient supply of calcium, phosphorus and vitamin D, and the Ministry recommends fat fish, fish livers, egg yolk, milk and butter (or margarine with vitamins added). Herrings, sprats and mackerel valuable.—Circular 1290, Ministry of Health, Recommendations to Maternity and Child Welfare Authorities (H.M.S.O. 1932).—*Brit. med. J.*, ii/1932, 848.

The criticism and improvement of diets.—Ministry of Health, Advisory Committee on Nutrition, London, H.M.S.O., 1932.

Diets in Poor Law Children's Homes.—*ibid.*, p. 17.

Diets for boys during the school age.—H. C. Corry Mann, *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 105, 1926.

Studies in nutrition. An enquiry into the diet of families in Cardiff and Reading.—E. P. Cathcart and A. M. T. Murray, *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 165, 1932.

The Schoolboy. A Study of his Nutrition, Physical Development and Health, by G. E. Friend, Med. Off. of Christ's Hospital, Horsham. W. Heffer & Sons, Ltd., 1935.

Other References to Nutrition

Qualitative and quantitative aspects of nutrition in relation to public health.—J. M. Hamill, *Nutr. Abstr. Rev.*, 1933-4, 1.

Food and the public health. The diet of the poor—white bread, margarine, skimmed milk, cheese, and tinned meat, cannot maintain vigour sufficient to ensure an adequate output of labour or resistance to attacks of illness.—W. J. Howarth, *Practitioner*, 1926, 188.

Proper nutrition is essential to healthy child-bearing and the diet throughout pregnancy and lactation should include a sufficiency of what are known as protective foodstuffs. When plenty of these are taken, there is every reason to

believe that the rest of the diet will take care of itself. As a general guidance the diet of pregnancy and lactation ought to include.

2 pints milk daily.

1 or 2 substantial servings of green vegetables.

1 or 2 eggs or egg yolks daily.

An apple, orange or some fresh fruit daily.

Sea fish twice or more a week.

Calf's liver once a week.

Cod-liver oil 2 teaspoonfuls daily.

—E. Mellanby, *Lancet*, ii/1933, 1137.

The food of the growing child.—R. Hutchinson, *Brit. med. J.*, i/1934, 439.

Diet in public schools. Allowance of butter should not be less than $1\frac{1}{2}$ oz per day and of milk $\frac{3}{4}$ pint daily and stone-ground flour (80%) made compulsory.—L. R. Lemprière, *Practitioner*, i/1926, 204.

A lecture on some surgical aspects of faulty nutrition.—R. McCarrison, *Brit. med. J.*, i/1931, 966. (The thyroid gland is more likely to be affected by faulty nutrition than any other organ.)

The Danish peasants' diet of 50 years ago, mainly consisting of dairy produce and vegetables, was the most healthy and by far the cheapest.—M. Hindhede, *Practitioner*, i/1926, 260.

Diet of whole wheat, milk, and sprouted legumes, far surpasses one of white bread, tea, sugar, and margarine.—R. McCarrison, *Brit. med. J.*, ii/1926, 730.

The criteria of an efficient diet.—Sir F. Gowland Hopkins, *Practitioner*, i/1926, 214.

The history of dietetics, R. Hutchinson, *Practitioner*, i/1934, 1.

A review of the progress in the physiology of nutrition.—W. J. Griffiths, *Nutr. Abstr. Rev.*, 1932-3, 205.

For references to bread and milk in nutrition see pp. 453 and 416 respectively.

ACCESSORY FOOD FACTORS, "VITAMINS"

A great amount of work has been done on the chemistry of the vitamins and on their estimation during the last five years. Four of them (A, B₁, C and D) have been prepared in an almost, if not quite, pure state, whilst the probable identity of lactoflavin with vitamin B₂ indicates that that factor also may soon be available in a pure form. Most workers recognise the existence of vitamins B₃, B₄, B₅, B₆ and a water-soluble factor Y, and still another one which was first detected in a particular form of caseinogen and has come to be known as the "casein factor." It may be identical with one detected in liver. Fresh workers have taken up the study of vitamin E.

The first International Conference on the Standardisation of the Vitamins was reported in Vol. I of the Extra Pharmacopœia. A second conference was held in June 1934, when the use which had been made of the standards since the first conference was discussed. Certain changes in the standards were made in accordance with the increased knowledge of the chemistry of the vitamins but the actual weight of a unit of each standard was adjusted so that the biological value of each unit remained unchanged.

The Estimation of Vitamins

Except for the chemical and physical tests for vitamin A and the chemical test for vitamin C, described in this section, all tests for vitamins have to be made biologically. Even the colour

tests and measurement of absorption at $328\text{ m}\mu$ for vitamin A can only be applied to substances which are easily saponified. The vitamin A content of other substances has to be estimated by biological tests. A biological estimation involves the simultaneous testing of the standard of reference, for animal reactions fluctuate from time to time to such an extent that no animal reaction at any time can be taken as an absolute measure of the activity of the dose given. It is only relative to the activity of the dose of standard tested simultaneously.

The Permanent Commission on Biological Standardisation of the Health Organisation of the League of Nations (1934) has recommended the adoption for international use of the following standards of reference:—

(1) **Vitamin A**—pure β -carotene in the form of a standard solution in oil, the strength of the solution being such that 1 gramme contains 500 International Units or 300 microgrammes (300γ) of β -carotene. The International Unit for vitamin A is defined as the vitamin A activity of 0.6 microgramme (0.6γ) of the International Standard Carotene. As the activity of 0.6γ of the new International Standard has the same vitamin A activity as 1γ of the provisional standard adopted in 1931, the unit of vitamin A activity remains unchanged.

The measurement of absorption at $328\text{ m}\mu$ expressed as $E_{1\text{ cm.}}^{1\%}$, and made under certain defined conditions, may be a reliable method for measuring the vitamin A content of liver oils and concentrates. As a means of converting values obtained for $E_{1\text{ cm.}}^{1\%}$ $328\text{ m}\mu$ into a figure representing the International Units of vitamin A per gramme of the material examined, the factor 1600 is recommended for adoption. It is desirable that, when a figure expressing the biological potency of a preparation has been derived by the use of this calculation, the fact should be stated.

(2) **Vitamin B₁**—the standard adsorption product of vitamin B₁ already in use. The International Unit recommended for adoption is the vitamin B₁ activity of 10 milligrammes of the International Standard adsorption product.

(3) **Vitamin C**—*l*-ascorbic acid. The International Unit recommended for adoption is 0.05 milligramme of *l*-ascorbic acid.

(4) **Vitamin D**—the standard preparation of irradiated ergosterol already in use. The International Unit recommended for adoption is the vitamin D activity of 1 milligramme of the International Standard solution of irradiated ergosterol.

Thus all the units of vitamin activity have the same biological values as those adopted after the 1931 Conference.

All the International Standard preparations of vitamins are kept at the National Institute for Medical Research, London.

The Biological Standardisation of Vitamins.—K. H. Coward, *Nutr. Abstr. Rev.*, 1934-5, 705.

Other Units for Vitamin Activity Still in Use. Various units of vitamin activity were used before the International Standards of Reference became

available. These units are still being used by some workers at the present day and "factors" are used for converting into international units, the results expressed in these units. The *U.S.P.* Revision Committee has suggested some of these factors, not with the purpose of encouraging the use of the old units but in order to give approximate values in international units of stocks of oils, already on the market, whose potencies have been stated in the old units. The *U.S.P.* Commission realises (as indeed do most other workers) that the old units were defined as a certain amount of animal reaction which itself varied from time to time and in different laboratories according to uncontrollable conditions. This means that an oil assayed at 100 "units" of vitamin D at one time might easily give a result of 200 "units" at another time or in another worker's laboratory. In contrast to this, the international units are particular weights of particular preparations of the vitamins. Thus an estimation of the vitamin content of a substance made by comparing the effect of a dose of that substance with the effect of a dose of a standard at the same time on similar animals is independent of the sensitivity of the rats at the time that the test is made. Within the limits of experimental error the same estimation of the potency of an oil should be obtained by different workers regardless of the details of the technique employed. By the time this edition of the Extra Pharmacopœia is published the international units only should be in use.

The Estimation of Vitamins other than Vitamins A, B₁, C and D. There are no standards of reference yet for any vitamins other than A, B₁, C and D, consequently there are no international units for these factors. Tests can be devised for comparing the vitamin content of two substances but great care must always be exercised to arrange the conditions of the test (diet, etc.), so that the results obtained depend only on the vitamin for which the test is being carried out.

The Accuracy Obtainable in Biological Tests for Vitamins. The "probable error" of vitamin tests is summarised in the following table (Coward, *Analyst*, 1934, 681).

Test						Probable error of an estimation when a simultaneous test on the standard is made, 20 animals being used in this test. Per cent.
Vitamin A, 5 weeks' test (male rats)	+25 or -20
" " 3 weeks' " (female rats)	+47 or -32
" " " (male rats)	+31 or -24
" " " (female rats)	+57 or -36
Vitamin B ₁ , Pigeons (percentage cured)	+44 or -30
" " (duration of cure)	+43 or -34
" " Rats (3 weeks test)	+9 or -8
Vitamin C	±20
Vitamin D	+19 or -17

For practical details of tests, see the section on each vitamin.

Mode of Action of the Vitamins

Some clinical use has been made of the pure or nearly pure forms of the vitamins.

Vitamin A. Deficiency causes a characteristic abnormality in certain cell structures, especially of mucous membrane cells and nerve cells.

Vitamin B₁. Deficiency prevents carbohydrate metabolism from proceeding normally, and lactic acid accumulates, which causes a slowing of the heart rate, and which, in the central nervous system, is responsible for the convulsive symptoms.

Vitamin C deficiency: the primary failure is in the function of certain highly active cells—e.g., odontoblasts, ameloblasts, etc.—and other changes observed are secondary to this primary effect.

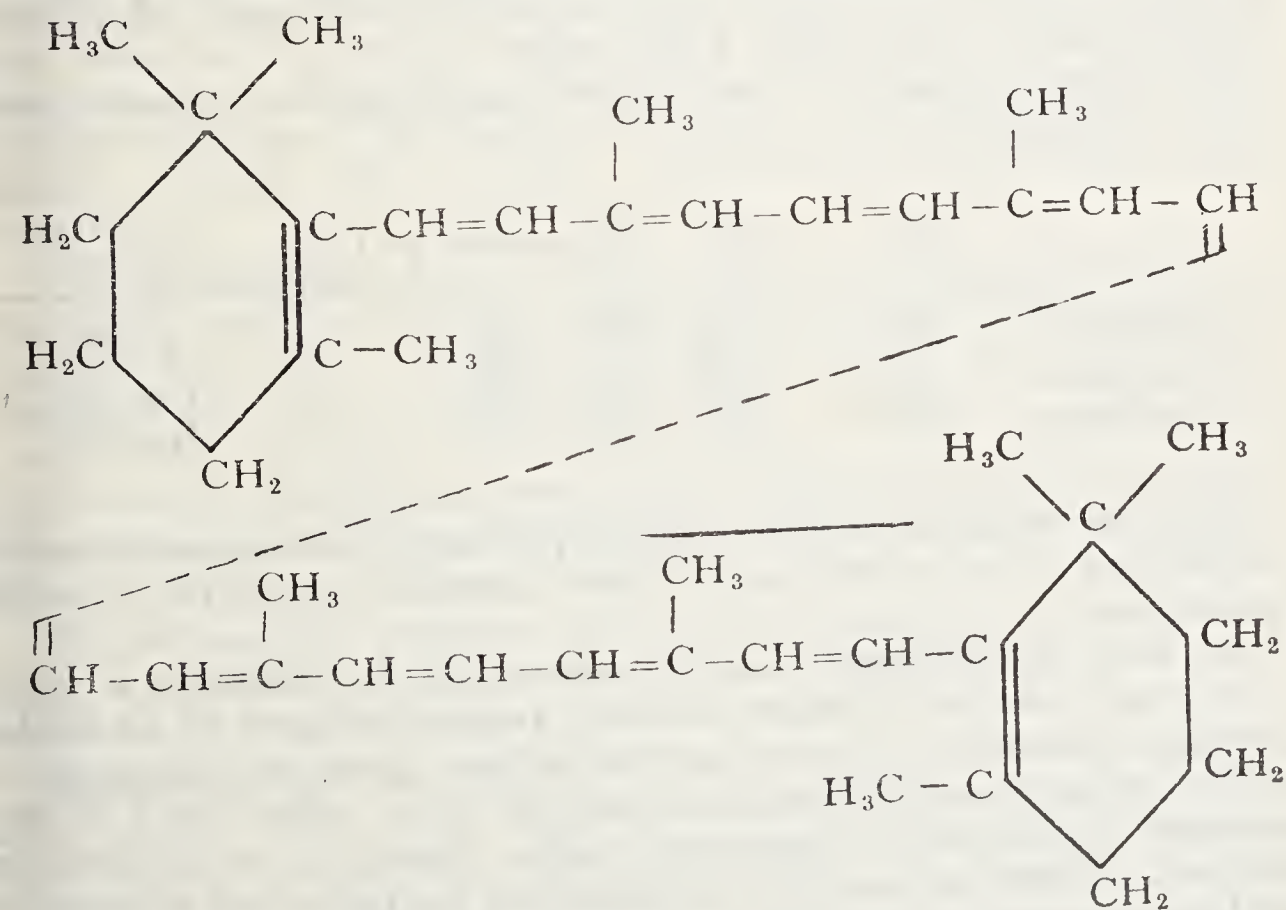
Vitamin D causes an increased “net absorption” of calcium or phosphate from the intestine, the level of the phosphate and/or calcium in the blood rises and as a mechanical result extra calcium phosphate is precipitated out into the bone. That is, the essential effect of vitamin D is to increase the assimilation of the food calcium and phosphate. (See L. J. Harris, *Brit. med. J.*, ii/1933, 371.)

Vitamin E. Deficiency causes degeneration of the tubules of the testes and resorption of the foetus.

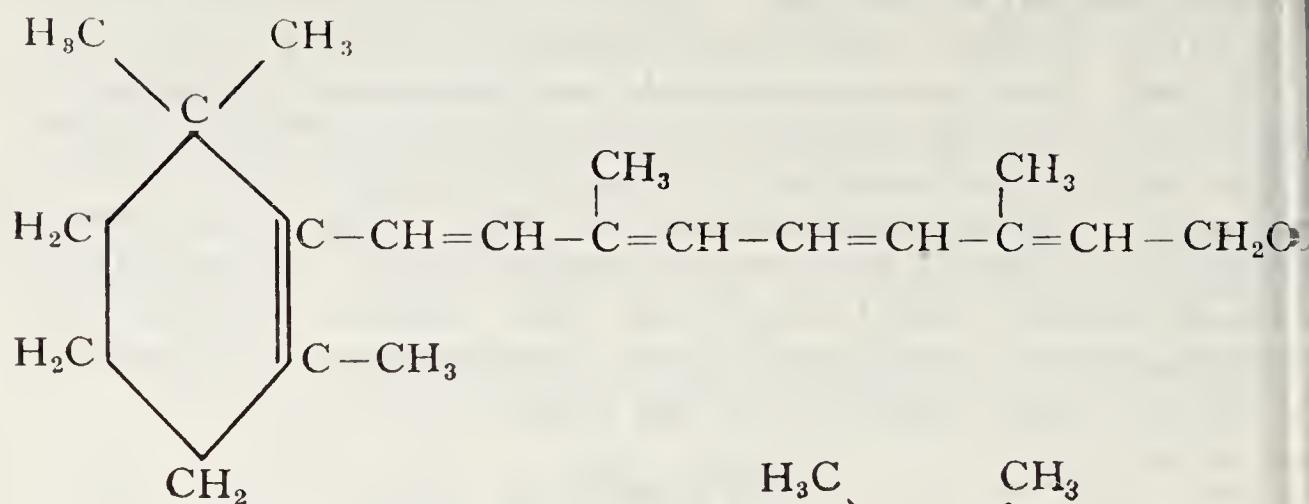
VITAMIN A

Chemistry of Vitamin A. The information available at the time of publishing Vol. I of the Extra Pharmacopœia has been supplemented somewhat. It has been shown that, weight for weight, β -carotene has about the same biological activity as the purest forms of vitamin A prepared. As its molecular weight is about double the molecular weight of vitamin A, it is probable that each molecule of β -carotene contains 2 active groups and that it splits into 2 molecules of vitamin A in the animal body.

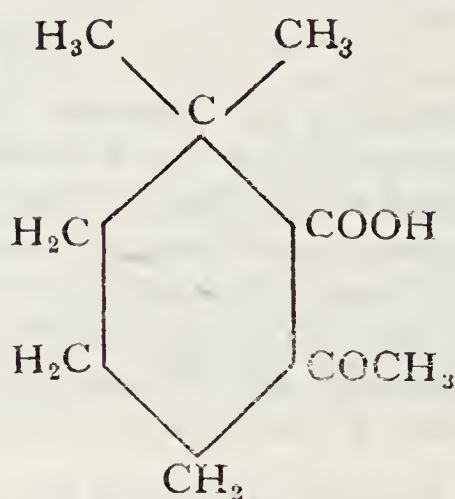
The formula accepted for β -carotene is



The formula accepted for vitamin A is



If geronic acid is written thus:—



it suggests how the decomposition of both β -carotene and vitamin A takes place when geronic acid is formed.—Karrer, Morf and Schöpp, *Helv. chim. Acta*, 1931, 1431.

The characteristics of the three carotenes are summarised in the following table:—

	M.p.	Max. Absorption in CS ₂	$[\alpha]_{814}$
α -carotene	183°	509, 477, 448	+ 323°
β -carotene	183°	520, 485, 450	Inactive
γ -carotene	174°	533, 496, 463	Inactive

Extracts of carotene from natural products contain much more β -carotene than α -carotene. They contain very little, if any γ -carotene.

α - and β -carotenes can be separated by filtering a light petroleum solution through a closely packed column of air-dried calcium hydroxide. A wide band of yellow β -carotene is retained in the column and below it, separated by a white band of the calcium hydroxide, a narrower yellow band of α -carotene is formed. These parts of the column can be taken out separately and the carotenes removed by suitable solvents.

The blue colour produced by the action of antimony trichloride on α -carotene gives only one absorption band i.e., 542 m μ . That produced by β -carotene also gives one only, at 590 m μ .

Highly concentrated vitamin A may also be separated into two fractions by absorption in a column of calcium hydroxide:—

(1) The α portion (a few per cent. only) which shows maximum absorption at $270\text{ m}\mu$.

(2) The β portion (the main portion) which shows maximum absorption at $328\text{ m}\mu$.

The blue colour given by antimony trichloride with the α portion shows at first only one band at $580\text{ m}\mu$. but soon shows a band at $620\text{ m}\mu$. The β -portion shows at once a band at $620\text{ m}\mu$.—Karrer, Walker, Schöpp and Morf, *Nature, Lond.*, ii/1933, 26.

Distilled Vitamin A. Very nearly pure vitamin A was prepared from the unsaponifiable fractions of very active halibut-liver oils by removing the sterols and distilling under very high vacua (0.00001 mm.). The main fraction (b.p. 137° to 138°) obtained by this method had a very high potency. Redistillation however, resulted in some loss of potency.

Similar preparations from sturgeon-liver oil and mammalian-liver oil gave spectrographic values at $328\text{ m}\mu$ in very good agreement with those of the preparation from halibut-liver oil and it therefore seemed that the preparations were identical. There was however, one point of disagreement. In halibut-liver oils, the ratio of the intensity of absorption at $693\text{ m}\mu$ to that at $617\text{ m}\mu$ of the antimony trichloride blue colour, varied according to the starting material from 0.1 to 0.25. In sturgeon-liver oil, this ratio was 0.25 at all stages of the extraction. In mammalian-liver oils, no band at all was detected at $693\text{ m}\mu$ either in the crude concentrates or in the purified distillates. This made the writers doubt whether any of their preparations were indeed pure vitamin A.

Distilled vitamin A is a pale yellow, viscous oil, mobile on warming, readily soluble in organic solvents, somewhat more so in methyl than ethyl alcohol. It was found to be unexpectedly resistant to aerial oxidation but highly susceptible towards acid media. On standing, even in the dark, losses of potency (as measured by the $328\text{ m}\mu$ band) up to 10% occurred in one month. The benzoate of vitamin A has been prepared.—Heilbron, Heslop, Morton, Webster, Rea and Drummond, *Biochem. J.*, 1932, 1178.

Kryptoxanthin, another lipochrome, has also been found to have vitamin A activity.—Kuhn and Grundmann, *Ber. dtsch. chem. Ges.*, 1934, 593.

Reactions of Vitamin A. The reaction of arsenic chloride or antimony chloride with fish-liver oil and concentrates (transient blue colour) is probably due to vitamin A, but other substances present in the natural oil interfere with the development of the blue colour to a variable extent. The test, therefore, can only be regarded as a qualitative one, or quantitative to a very limited extent, viz., an oil giving a deep blue colour is probably rich in vitamin A, one giving a faint blue, or no blue at all, is probably

nearly or quite devoid of vitamin A. But of two oils giving the same colour value, one may contain four times as much vitamin A as the other when measured biologically.

The blue value of a concentrate runs more nearly parallel with the biological value than the blue value of the oil itself. The best method of preparing the unsaponifiable fraction of an oil is that recommended by the Permanent Commission on Biological Standardisation. (See Evers and Smith, *Quart. J. Pharm.*, 1933, 477).

Spectroscopic Estimation of Vitamin A. Vitamin A in fish-liver oils and in concentrates shows selective absorption at 328 m μ . The intensity of absorption at this wave-length of concentrates and of oils of more than 10,000 International Units of vitamin A per gramme may be taken as a quantitative estimation of vitamin A. Cod-liver oils contain substances which interfere with the measurement of absorption and, therefore, the vitamin A in cod-liver oils should be measured in the unsaponifiable fraction of the oil, not on the oil itself. The measurement is made by a spectrophotometer. It is always made on a 1% solution in alcohol or in cyclohexane (chloroform is unsuitable) contained in a quartz cell through 1 cm. depth of solution. The result is expressed as the value $E_{1\text{ cm.}}^{1\%}$. It is the value of $\log I_0/I$ where I_0 is the incident light and I is the emergent light, e.g., a 1% solution of a concentrate in alcohol transmitted 5% of the incident light and absorbed 95%. Its value is, therefore, $I_0/I = \log \frac{100}{5} = 1.301$. An oil that transmitted 10% and absorbed 90% of the incident light would have the value $E_{1\text{ cm.}}^{1\%} = \log \frac{100}{10} = 1.0$.

Stability of Vitamin A. Vitamin A survives the high temperatures of distillation of concentrates, 137° under 0.00001 mm. pressure. The purest concentrates are also highly resistant to aerial oxidation at high temperatures. In other media the vitamin is easily destroyed.

The cooking of vegetables by the usual methods adopted in households destroys very little, if any, vitamin A.—Morgan (unpublished results).

While the vitamin in butter is not diminished by exposure to 120° for 4 hours it is in the same period greatly diminished and in 12 hours completely destroyed if the butter is thoroughly aerated during the heating, i.e., one must conclude that, though fairly resistant to heat, this vitamin is readily destroyed by oxidation.—*Brit. med. J.*, i/1921, 237; i/1922, 236. Heating at 120° and 32 hours aeration destroys it.—E. Mellanby, *Brit. med. J.*, i/1924, 895.

Ozone, even in the dark, destroys vitamin A.—S. S. Zilva, *Brit. med. J.*, i/1925, 1110.

Vitamin content of Australian, New Zealand and English butters.—M. E. Crawford, E. O. V. Perry and S. S. Zilva, *Spec. Rep. Ser. med. Res. Council Lond.*, No. 175, 1932.

Effect of Solvents on Vitamin A Potency

Solutions containing 0.2 mg. of carotene per millilitre, with and without 0.01% of hydroquinone per millilitre, were stored in tightly stoppered test-tubes at 20°. The best results were obtained with cottonseed oil as solvent, with which there was a loss of 10% in 5 months, while olive, corn and coconut oils caused 20% loss in 5 months.

50% destruction, not lessened by hydroquinone. With cottonseed oil at 4°, it exposed for 5 minutes daily to air and light to simulate the exposure during feeding tests, the loss during 5 months was 48%. Organic solvents were unsatisfactory. Destruction of the carotene can occur either by oxidation or by conversion to achroocaratene.—C. A. Baumann and H. Steenbock, *J. biol. chem.*, 1933, 101, 561.

A solution of 0.2% of carotene in olive oil containing 0.1% of hydroquinone loses approximately half its vitamin A potency in a year; the effects of light and temperature are described.—R. G. Turner, *J. biol. Chem.*, 1934, 105, 443.

The choice of solvent is of importance in connection with the vitamin A activity of carotene and cod-liver oil.—F. J. Dyer, K. M. Key and K. H. Howard, *Biochem. J.*, 1934, 875.

Estimation of Vitamin A. Vitamin A is generally estimated by its power to make rats resume growth after they have ceased to grow on a diet containing all factors known to be necessary for growth except vitamin A. A diet suitable for this purpose consists of:—

Caseinogen	15%
Dextrinised rice starch	73%
Dried brewers' yeast	8%
Salt mixture (Steenbock's 40)	4%

In addition, 8 to 10 units of vitamin D per week are given to each rat, for vitamin D is essential to growth as well as to calcification of bone.

Steenbock's salt mixture consists of:—

Sodium chloride, NaCl	23.4 grammes
Magnesium sulphate, $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$	24.6 "
Disodium hydrogen phosphate, $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$	35.8 "
Dipotassium hydrogen phosphate, K_2HPO_4	69.6 "
Calcium phosphate, $\text{Ca}_2\text{H}_2(\text{PO}_4)_2 \cdot 4\text{H}_2\text{O}$	68.8 "
Calcium lactate, $\text{C}_6\text{H}_{10}\text{O}_6\text{Ca} \cdot 5\text{H}_2\text{O}$	15.4 "
Iron citrate, $\text{C}_6\text{H}_5\text{O}_7\text{Fe} \cdot 6\text{H}_2\text{O}$	6.0 "
Potassium iodide, KI	0.16 gramme

Some workers add 15% of a hydrogenated vegetable oil to the basal diet but this is not necessary.

Young rats weighing about 30 g. are given the above diet until they cease to grow. They are weighed once a week for about 4 weeks, then two or three times a week. As they become steady in weight, they are divided into groups, two groups for different doses of the International Standard and two or three groups for different doses of the test substance. If no information is available concerning the probable potency of the substance under test, three different doses, in the ratio of 1 : 3 : 9, should be tested against two doses of the standard in the ratio of 1 : 3. A group of about five rats should be used for each dose, all the rats of any one group being given the same dose. By comparing the average responses in, say, 3 weeks, of the different groups of rats, some idea of the potency of the substance will be gained. A further test with fewer doses differing less widely will give more accurate information of the potency.

Convenient daily doses of a sample of cod-liver oil are 0.5 mg., 1.0 mg. and 2.0 mg., and of the International Standard, 1.0 and 2.0 units respectively. It is possible that the response from 0.5 mg. cod-liver oil would correspond to the response from 2.0 units of the standard. The potency of the oil would then be 4000 international units per gramme. If the response from 0.5 mg. of cod-liver oil corresponded to the response from 1.0 unit of the standard, and that from 1.0 mg. of cod-liver oil corresponded to that from 2.0 units of the standard, then the cod-liver oil would contain 2000 International Units per gramme. If 2.0 mg. of cod-liver oil corresponded to 1.0 unit of the standard then the oil would contain only 500 International Units per gramme. It is very improbable that the average responses of one pair of groups (one cod-liver oil and one standard) would give exactly the same estimate of the potency of the cod-liver oil as the average responses from another pair of groups. The two (or three) estimates should be averaged to obtain a fair idea of the potency of the oil.

It is essential to dilute the cod-liver oil with the same oil that is used for dissolving the standard. Coconut oil and arachis oil have been found suitable diluents.

An economy of animals and labour may be effected if many tests are to be carried out by first constructing a "*curve of response.*" Five groups of about 12 rats each (6 male and 6 female), prepared as described above, are given daily doses of 0.5, 1.0, 2.0, 4.0, and 8.0 mg. respectively of a particular sample of cod-liver oil, every rat in any one group being given the same dose. At the end of the test period (say, 3 weeks), the average gains in weight of the different groups are found and plotted against the dose of cod-liver oil given. The resulting curve will probably be logarithmic. It is then used as follows. In every fresh test, one group of 8 to 10 rats prepared in the usual way is given a daily dose of, say, 1 mg. of cod-liver oil; another group of rats prepared in the same way is given a daily dose of, say, 2 units of the standard. The mean increases in weight in 3 weeks of the different groups of rats are calculated. The abscissa of the curve corresponding to each mean increase in weight is found. The ratio of these two abscissæ gives the ratio of the vitamin A potency of the doses of cod-liver oil and standard respectively, from which may be calculated the vitamin A potency of the oil. It should be stated as a number of International Units of vitamin A per gramme of cod-liver oil.

The curative method of assay for vitamin A involves a preliminary depletion period which causes variable pathological symptoms and, in consequence, serious discrepancies.—J. B. Orr and M. B. Richards, *Nature, Lond.*, i/1934, 255.

For a brief descriptive account of the chemical methods used for the evaluation of the vitamins see A. L. Bacharach and E. L. Smith, *Analyst*, 1934, 70.

For the vitamins of cod-liver oil see Ol. Morrhuæ, p. 164.

CLINICAL WORK ON VITAMIN A

Vitamin A as an "Anti-infective" Agent

The infections found in vitamin A deficiency are of a special type, limited in origin to epithelial tissues. They are attributable to deficient secretion of mucus and desquamation. With provision of vitamin A, epithelium becomes normal.

again and the local infections disappear, but if avitaminosis is continued the local infections spread, the destruction of the epithelium causing absorption of infecting micro-organisms, and septicæmia may result. The ensurance of adequate vitamin A diets is therefore important, but existing data show no basis for the belief that vitamin A therapy is effective in combating general infections.—L. J. Harris and co-workers, *Lancet*, i/1932, 615.

Vitamin A determined in over 300 human livers, at autopsies, by the antimony trichloride method. Adequate reserves were frequently observed in a wide variety of infective conditions, and it is therefore plain that vitamin A should not be regarded as a positive anti-infective agent, indiscriminate in action. The term 'anti-infective' is only justifiable as complementary to the fact that vitamin A deficiency leads to subnormal powers of resistance.—T. Moore, *Lancet*, ii/1932, 669.

Is *not* a general anti-infective agent; it is anti-infective only in a limited way and vitamin A therapy has failed to have any effect as a prophylactic in respiratory diseases, in the common cold in infants, on the incidence of common infections generally, or in treatment of pneumonia. The local infections to which vitamin A deficiency gives rise are of quite a special type, being caused by structural breakdown of membranes; there is no change in the general immunity.—L. J. Harris, *Brit. med. J.*, ii/1933, 231.

An experiment consisting in the administration over a period of 6 months of a concentrate of vitamins A and D, in daily doses equivalent in vitamin A to rather more than 1 oz. of high-grade cod-liver oil, to 294 poor schoolchildren of Peterhead, with 281 contemporaries acting as controls, showed the rate of growth of the treated children as only slightly better than that of the controls and *susceptibility to infection and resistance to established disease were apparently unaffected*. The results compared unfavourably with milk experiments. Evidence suggested that the cause of the failure was that the vitamin supplements made good only one dietary deficiency and left uncorrected associated deficiencies of equally essential constituents of the diet. The public must be educated that vitamin supplements do not constitute a short cut to health but that a well-balanced dietary is essential.—R. Sutherland, *Brit. med. J.*, i/1934, 791.

The fat-soluble vitamins—their significance in nutrition.—E. Mellanby, *Edinb. med. J.*, 1933, 40, 197.

The addition of vitamin A to an artificial diet for babies which is generally considered to contain enough of this factor, had no influence on the general health, rate of gain in weight, or on the general resistance to infection, whether of the respiratory or digestive tract or to specific fevers. It did, however, diminish the incidence of minor "infective" skin lesions (sore buttocks, intertrigo, etc.). It is probable that a slight vitamin A deficiency is a common occurrence in artificially-fed babies in this country unless the vitamin is specifically added to their diet by the administration of cod-liver oil or some other potent source of vitamin A.—Helen M. M. Mackay, *Arch. Dis. Childh.*, 1934, 133.

Dentition

Insufficient vitamin A in the diet may lead to overgrowth and abnormality of the soft tissues surrounding the teeth (pyorrhœa). A deficiency of vitamin A (and of vitamin D also) is of much greater significance during the early years of life when the tissues are developing than the same deficiency after the periodontal tissues are developed.—May Mellanby, *Proc. R. Soc. Med.*, 1930, 41.

Perfectly calcified and regularly arranged teeth can be produced by including in the maternal diet during pregnancy and lactation, and in the diet of the offspring at the time of dental development, substances containing much fat-soluble vitamin, calcium and phosphorus. Cereals, especially oatmeal, tend to produce badly developed (hypoplastic) teeth and call for a correspondingly larger supply of calcifying foods. The teeth of the majority of children in the British Isles are imperfect in structure and have a roughish surface: dental caries is more likely to attack such teeth than perfect teeth with normal enamel and dentine and a comparatively smooth surface. The resistance of teeth to caries can be increased independently of their original structure by giving a diet of high calcifying activity, while resistance is decreased by a diet rich in cereals and of low calcifying properties. Deficiency of vitamin A or carotene plays an important part in development of periodontal tissues and control of onset of periodontal disease, including pyorrhœa.—May Mellanby, *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 191, 1934; *Brit. med. J.*, i/1934, 252.

Puerperal Sepsis

A daily dose of a concentrate of vitamins A and D was given to half of 556 maternity cases during the latter part of pregnancy; none was given to the other half. 1.1% of those receiving the concentrate and 4.7% of the controls developed puerperal sepsis of the B.M.A. standard of morbidity.—H. N. Green, D. Pindar, G. Davis and E. Mellanby, *Brit. med. J.*, ii/1931, 595.

In twenty cases of puerperal sepsis treated with large doses of vitamin A, low vitamin A reserves were found in several cases, indicating that in degenerated conditions of the liver the liver cells are unable to retain the vitamin.—H. N. Green, *Lancet*, ii/1932, 723.

Respiratory Infections

A group of workers who were given a tablespoonful of cod-liver oil daily as a supplement to their ordinary dietary had fewer colds and altogether lost 40% less time through ill-health than the control group which received no supplement.—A. D. Holmes, M. G. Pigott, W. A. Sawyer, and L. Comstock, *Industr. Engng Chem.*, 1932, 24, 1058.

Seven hundred and sixty-four cases of lobar pneumonia in S. African mine workers were divided into two groups, alternate admissions to hospital being distributed to the two groups respectively. The members of one group were given large doses of a vitamin A concentrate, those of the other were given no addition to the ordinary hospital dietary. No difference in the course of the disease in the two groups could be found, whether judged by mortality rate, length of stay in hospital, condition on discharge or incidence of sequelæ. Temperature came down by crisis in a higher percentage of the treated than of the untreated cases.—A. J. Orenstein, *S. Afr. med. J.*, Nov. 12, 1932, 16.

Vision

Night blindness may be used for detecting moderate degrees of vitamin A deficiency. Visual tests were made with a Buch-Hirschfeld photometer on 213 children and moderate degrees of night blindness were found in 45. Recovery was induced by dosing with cod-liver oil for an average of 12 days.—P. C. Jeans and Z. Zentmire, *J. Amer. med. Ass.*, i/1934, 892.

The incidence of xerophthalmia and night blindness in the United States. A gauge of vitamin A deficiency.—*Amer. J. publ. Hlth*, 1933, 935. (Incidence almost nil.)

Carotenoids and the vitamin A cycle in vision.—G. Wald, Kaiser Wilhelm Institut, Heidelberg and Univ. of Chicago, *Nature*, ii/1934, 65.

Regeneration of the visual purple is more rapid in rats receiving abundant supplies of vitamin A in their diet than in those deprived of vitamin A.—K. Tansley, *J. Physiol.*, 1931, 71, 442.

A survey of the relation of vitamins A and D to keratomalacia, dental caries, rickets, bone calcification, infection, and nerve degeneration.—E. Mellanby, *Edinb. med. J.*, 1933, 197.

Measles

Vitamin therapy (vitamins A and D) was found to be ineffective in combating the measles epidemic of 1931-2.—*Report of the M.O.H. and S.M.O., London County Council*, 1933, p. 91.

Phosphatic Calculi

A lecture on the causation of stone in India.—R. McCarrison, *Brit. med. J.*, i/1931, 1009. Deficiency of vitamin A and a diet with high calcium but low phosphorus content tend to produce stone.

Experiments with rats indicate some connection between deficiency in vitamin A and formation of phosphatic calculi.—Prof. E. C. van Leersum, B.M.A. 1927, per *Brit. med. J.*, ii/1927, 874.

Gastric lesions occurred in rats fed on synthetic diets in which the only deficiency was want of vitamin A.—Pappenheimer and Larimore, quoted by McCarrison, *Brit. med. J.*, i/1925, 359.

From data obtained from 957 specimens of human liver from persons killed by accident or dying from acute diseases there is good reason to believe that 16% of the population of the Netherlands have definitely subnormal vitamin A reserves. In cases of chronic diseases this amounted to 24.2%.—L. K. Wolff, *Lancet*, ii/1932, 617.

VITAMIN B₁

Chemistry of Vitamin B₁. Vitamin B₁ (the antineuritic factor) has been prepared in an almost, if not quite, pure form. Crystalline compounds with hydrochloric, nitric, and sulphuric acids have been prepared. The chemical formula of the hydrochloride is probably C₁₂H₁₇O₂N₄S, 2HCl, or possibly C₁₂H₂₀O₂N₄S, 2HCl. The base gives a positive nitroprusside reaction only after fusion with alkali. It is precipitated by phosphotungstic acid at pH 4.0 to 5.0, by mercuric chloride, silver nitrate plus baryta, picrolonic acid, gold chloride, platinic chloride and Dragendorff's reagent. It gives a yellow colour with Pauly reagent.—Kinnersley, O'Brien, Peters and Reader, *Biochem. J.*, 1933, 225.

Crystals of high vitamin B₁ activity prepared from yeast may be mixtures of active and inactive vitamin B₁. 2000 kilograms of bakers' yeast gave approximately 500 mg. of crystals.—H. W. Kinnersley, J. R. O'Brien and R. A. Peters, *Biochem. J.*, 1933, 232.

Crystals of the hydrochloride prepared from different sources have all been shown to be substantially identical in form and in X-ray patterns.—Bernall and Crowfoot, *Nature, Lond.*, i/1933, 911.

Stability of Vitamin B₁. In faintly acid or in acid media, the resistance of vitamin B₁ to heat is considerable. In baking bread or biscuits, when the temperature of the interior of the loaf does not rise above 100°, no serious diminution in vitamin B₁ content may be expected. Crude concentrates of vitamin B₁ have been kept in 99% alcohol at pH 1.0 to 2.0 at room temperature for 3 years, but some highly purified preparations gradually lost their activity under these conditions.

Alkalis, on the other hand, cause ready destruction of vitamin B₁ even at low temperatures. It is not oxidised by exposure to air or ozone. In acid solution it is stable to hydrogen peroxide, and to potassium permanganate.

Treatment with nitrous acid has no effect on it, which is regarded as strong evidence that the vitamin is neither a primary nor a secondary amine.—*Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 167, 1932.

Sources of Vitamin B₁. Oranges, watercress, lettuce, spinach, and cabbage are rich sources of vitamin B₁ (the B₂ content is definitely lower).—*Lister Inst. Rep.*, 1932; *Brit. med. J.*, ii/1932, 23. Milk and dried yeast are rich sources.

Estimation of Vitamin B₁. Vitamin B₁ is estimated either on pigeons or on rats. There is a certain amount of evidence that some substances (e.g., dried yeast) do not give the same result when estimated on rats as they do when estimated on pigeons. The cure of retracted neck in pigeons must be considered a more specific test for vitamin B₁ than the resumption of growth in rats which have ceased to grow on a deficiency of that factor. The pigeon test, therefore, probably gives a truer value of the vitamin B₁ content of a substance than the rat growth test.

The estimation of vitamin B₁ by the use of pigeons is carried out as follows:—

About a hundred pigeons are given a diet of polished rice in cages provided with open wire mesh screens to prevent the birds from having access to their faeces. The faeces often

contain vitamin B₁ even when the diet does not and pigeons and rats will eat their own fæces when otherwise deprived of that factor. Fresh water is given daily. In 3 to 4 weeks many pigeons fed on a diet of polished rice will develop retracted neck, quite suddenly and generally overnight. Two or three doses of the substance under examination should be tested against one or two doses of the standard. Generally a dose of 30 mg. of the standard will produce a cure in 50% of the birds used for this test. In any test in which the result is necessarily either positive or negative (e.g., cure of retracted neck or failure to cure retracted neck; death of the animal or recovery of the animal) it is desirable to aim at a comparison of doses which bring about a 50% positive result. Thus it should be the aim in a test for vitamin B₁ in pigeons to discover the dose of test substance and of standard which, in the particular lot of pigeons used, will both bring about 50% of cures in the groups of birds given those doses. Eight or ten birds should be used in each group. Often only about half of the pigeons given the diet of polished rice develop retracted neck; therefore it is necessary to start with about twice as many pigeons as it is proposed to use in the test.

Comparison of the duration of cure of the same pigeons may also be made, and will, within the limits of experimental error, give the same result as the comparison made by the percentage of birds cured.

Curves of response may be constructed for this test in the same way as the curve of response for the estimation of vitamin A, if many estimations of vitamin B₁ are to be made. When this has been done one dose of the standard only need be tested simultaneously with the test of one dose of the substance under examination. The results are then calculated as in the vitamin A test.

The estimation of vitamin B₁ by the growth response of rats is carried out as follows:—

Young rats of about 50 g. weight are given a diet containing all factors known to be necessary for growth except B₁. A suitable diet for this purpose consists of:—

Caseinogen	15 parts by weight
Dextrinised rice starch	79 „ „
Salt mixture (Steenbock's 40)	4 „ „
Agar	2 „ „
Dried yeast autoclaved at 120° for 6 hrs.	25 „ „

In addition about 5 drops of a good sample of cod-liver oil are given to each rat directly into its mouth, twice a week, to supply vitamins A and D. Dried brewers' yeast autoclaved at 120° for 6 hours appears to contain no vitamin B₁ and, when added as 25% to the diet, it supplies enough of all the other B vitamins for growth. Throughout the whole test the rats' cages are provided with wire mesh grids to prevent the rats from having access to their fæces.

Rats fed on this diet will cease to grow in 2 to 3 weeks. As the rats become steady in weight, they are divided into the required

number of groups, each rat being put in a separate cage. The rats' response to vitamin B₁ is less variable than the pigeons' response and it is only necessary, therefore, to have 4 or 5 rats in each group. Doses of the standard suitable for the test are 10 and 20 mg. respectively. The doses of the substance under examination must be chosen according to its probable potency, the aim being to find one or two doses of the test substance which will give approximately the same result as one or two doses respectively of the standard. Calculations of the potency of the test substance in international units can then be made.

Curves of response for vitamin B₁ tests may be constructed in the same way as the curves of response for vitamin A tests if many estimations are to be carried out. Five groups of about 6 rats (3 males and 3 females) in each group are given graded doses of the International Standard. The average results for the groups are plotted against the dose of standard given. When this has been done, one dose only of the standard needs to be tested simultaneously with one dose of the substance under examination. The results are then calculated as in the vitamin A test.

VITAMIN B₂

(Known as vitamin G in America)

Chemistry of Vitamin B₂.

Vitamin B₂ may be identical with lactoflavin or ovoflavin.—György, Kahn and Wagner-Jauregg, *Naturwissenschaften*, 1933, 30, 560. The so-called "vitamin B₂" may consist of two parts, (a) a flavin for which the name vitamin B₂ may be retained, and (b) another substance which may be called vitamin B₆, which is probably the antipellagra factor.—P. György, *Nature, Lond.*, 1934, 498. A paper on the "Lyochromes" (to which the flavins belong) by Ellinger and Koschura appeared in *Nature, Lond.*, i/1934, 553.

Stability of Vitamin B₂. Vitamin B₂ is much more heat stable than vitamin B₁ but is by no means completely so. The autoclaving of yeast to destroy B₁ always destroys a part of B₂ also. Both vitamins B₁ and B₂ are affected by ultra-violet light, the latter more than the former.—*Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 167, 1932, pp. 152-4.

Therapeutic use of vitamin B₂

Current theories of the ætiology of pellagra. Arguments for and against the theories that pellagra is due to (a) deficiency of some amino-acid; (b) deficiency of vitamin B₂; and (c) a toxic substance in maize whose effects are corrected by sufficient good protein or by vitamin B₂, are examined.—Chick, *Lancet*, ii/1933, 341.

Pellagra, by W. R. Aykroyd, *Nutr. Abstr. Rev.*, 1933-4, 12.

From the theoretical point of view it would seem that vitamin G (B₂), so far as it plays a rôle in the syndrome of pellagra, may be of far more value as a prophylactic measure than as a curative agent.—F. P. Underhill, *J. Amer. med. Ass.*, ii/1932, 123.

For further references to pellagra see *Bacteriological Notes*, p. 575.

Swift's or pink disease in six cases in children aged 15 months to 4½ years showed rapid improvement on treatment with liver or liver extract.

VITAMIN B₃

Chemistry of Vitamin B₃. Little is known of this factor beyond the fact that "something" occurring in dried yeast and wheat embryo is necessary to prevent loss of weight in pigeons fed on a diet of polished rice supplemented with liberal amounts of vitamin B₁.

Stability of Vitamin B₃. This factor is thermolabile.—*Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 167, 1932, pp. 165-6.

VITAMIN B₄

Chemistry of Vitamin B₄. This factor is found in bakers' yeast and can be separated from the watery extracts of vitamin B₁ by adsorption on Norite charcoal at pH 1.0. It is a base and forms a crystalline hydrochloride of the composition C₄H₄N₄.HCl, $\frac{1}{2}$ H₂O. It is precipitated by phosphotungstic acid (pH 2.0 to 4.0), mercuric sulphate, picric acid, picrolonic acid and gold chloride. Pauly and nitroprusside tests are negative.—Kinnersley, O'Brien, Peters and Reader, *Biochem. J.*, 1933, 225.

Symptoms of vitamin B₄ deficiency in rats are different from the symptoms of B₁ deficiency. Vitamin B₄ has not yet been shown to be necessary for human beings.

Stability of Vitamin B₄. Vitamin B₄ is thermolabile. It is most stable in 20% acetone-water solution at pH 3.0.

VITAMIN B₅

Chemistry of Vitamin B₅. No attempt has been made to isolate this factor. Its existence is postulated by Randoin and Lecoq, who fed their pigeons artificially on a diet more nearly complete than is a diet of polished rice. Hence it is difficult to compare their results with those of other workers.

Stability of Vitamin B₅. Vitamin B₅ is more heat stable than vitamin B₁. *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 167, 1932, pp. 166-7.

FACTOR γ

Chemistry of Factor γ . Factor γ was recognised by Chick and Copping (*Biochem. J.*, 1930, 1744) through the inability of rats to grow on a diet, supposed to be complete, containing B₁ in the form of Peters' purified concentrate from yeast and B₂ in a preparation from egg white. When B₂ was supplied as an auto-claved yeast extract growth was always improved. It was distinguished from all other components of the B complex by its greater stability to heat.

Stability of Factor γ . Factor γ in watery yeast extracts resists heating at 120° to 125° in alkaline solution for 4 hours at pH 9 to 10.

Occurrence of Factor γ . Factor γ is absent from, or present in only small amounts in, onion, meat (ox muscle), wheat embryo and egg white and is present more abundantly in yeast, ox liver, egg yolk, and green-leaf vegetables.

THE "CASEIN FACTOR"

Strong evidence of the existence of still another vitamin necessary for growth was found by Coward, Key and Morgan (*Biochem. J.*, 1929, 695). It was first detected in a particular form of casein (light, white, B.D.H.) and later found in milk (as was to be expected), in lettuce, wheat embryo, liver and, to a less extent, in lean meat. It was absent from dried yeast, marmite, etiolated wheat shoots, agar, etc. It was almost impossible to extract it from casein or wheat embryo. It is probable that it is identical with "physin," a substance found to be necessary for growth of the young rat and present in liver.—Mapson, *Biochem. J.*, 1932, 970 and 1061.

THERAPEUTIC USE OF VITAMIN B (COMPLEX)

Chronic vitamin B deficiency—67 cases of patients with constipation, colitis, asthenia and malnutrition were given about 15 g. of wheat germ daily. Marked improvement followed, noticeable within a few days or weeks. In a few cases other measures had to be adopted, possibly because prolonged deficiency had left a varying amount of irreparable damage to the intestinal tract.—H. E. Marks, *Med. J. Rec.*, 1932, 135, 231.

Bran, leached bran, and filter paper were found to be laxative both for rats and humans, but the ash of bran was without influence.—M. S. Rose, *et al.*, *J. Amer. diet. Ass.*, 1932, 8, 133.

There is no compelling evidence for the widely advocated theory that the prevalence of constipation in this country is due to vitamin B shortage.—L. J. Harris, *Brit. med. J.*, ii/1933, 232.

The vitamin B complex (B₁, B₂, B₃) favours the glycogenic function of the liver and increases its content of oxido-reducers. In diabetics it lessens the glycosuria and glycaemia, increases tolerance for carbohydrates, improves general condition and increases weight. At commencement of treatment insulin should be given but may later be decreased or discontinued.—M. Labbé and co-workers, per *Brit. med. J. Epit.*, ii/1933, 45.

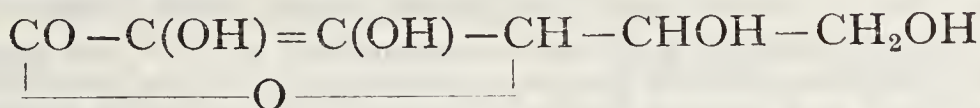
It seems clear that vitamins B₁, B₂ and B₄ have no hæmopoietic effect.—Lucy Wills, *Brit. med. J.*, ii/1933, 1170.

For the therapeutic use of vitamin B in beri-beri, see p. 514.

VITAMIN C

The Chemistry of Vitamin C. Szent-Györgyi has isolated vitamin C from the suprarenal glands and from various fruits and vegetables. It has been analysed and also synthesised, and is thus the most clearly defined vitamin at present.

Its formula is:—



It has been named ascorbic acid and is described in *New and Non-Official Remedies* under the name of Cevitamic Acid. It shows a characteristic absorption band in the ultra-violet at 245 m μ in aqueous acid solution.

Ascorbic acid has strong reducing properties. Thus its concentration in fruit juices may be measured by means of a N/1000 (or M/2000) solution of 2 : 6 dichlorophenolindophenol. This reaction is, however, not specific, glutathione and cysteine giving the same reaction, but in juices which are known not to contain these substances, the reaction may replace the more laborious biological one for the estimation of vitamin C.—Svirbely and Szent-Györgyi, *Nature, Lond.*, i/1932, 576; Ault and co-workers, *J. chem. Soc.*, 1933, 1419.

A report of the discussion on the chemistry of vitamin C at the British Association, 1934, was given in *Nature, Lond.*, ii/1934, 724.

Development of the discovery of the identity of vitamin C and ascorbic acid.—A. Szent-Györgyi, *Nature, Lond.*, i/1933, 225.

The antiscorbutic activity of ascorbic acid is due to the acid itself and not to any adherent matter. When the diet is free from vitamin C, ascorbic acid is used up from the suprarenal glands.—J. L. Svirbely and A. Szent-Györgyi, *Biochem. J.*, 1933, 279.

Stability of Vitamin C. Ascorbic acid is stable in aqueous acid media at ordinary temperatures. In the dry state it is also stable in air.—Ault and co-workers, *J. chem. Soc.*, 1933, 1419.

Vitamin C in fruit juices is sensitive to oxidising agents and air. In alkaline solution it is stable under anaerobic conditions, but in the presence of air it is rapidly destroyed.—*Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 167, 1932, p. 199.

Titration with 2 : 6-dichlorophenolindophenol shows a variation in ascorbic acid content of both fresh lemon and orange juices. The method has been used to test the value of preservatives and sterilisation. Fresh filtered lemon juice pasteurised for 1 hour at 65° lost all its reducing power in 12 days when left exposed to air. The same juice treated with sulphur dioxide, instead of being pasteurised, completely lost its reducing power in 26 days when there was access of air. Sealed out of contact with air, the juice retains its activity very much longer when pasteurised or preserved with sulphur dioxide.—A. H. Bennett, *Analyst*, 1934, 91.

By the titration method it has been shown that the reducing power of orange juice is higher and more constant than lemon juice; and, in storage with preservatives to prevent fermentation, the reducing power may disappear completely in a few weeks. Acid and heat produce the same effect and it is believed that an enzyme present in the untreated juice protects the vitamin from oxidation.—A. H. Bennett and D. J. Tarbert, *Biochem. J.*, 1933, 1294.

The **vitamin C value of milk** decreases rapidly on standing under ordinary conditions.—S. K. Kon, *Nature, Lond.*, ii/1933, 64.

Pasteurisation of milk at 145°F. for 30 minutes lowers the vitamin C content.—Hamill, *Lancet*, ii/1923, 339.

Heating milk for half an hour at 63°C is worse than 15 minutes at 85°C.—*J. Amer. med. Ass.*, ii/1925, 2002.

Dried milks probably contain no vitamin C.

Prolonged **boiling of vegetables**, as in the making of stews, destroys nearly all the vitamin C.

If canned vegetables and fruit are sealed before being subjected to heat, thus reducing oxidation, all the vitamins are at least partially preserved.

Light also appears to have a destructive action on vitamin C independently of any heat effect.—Mattick and Kon, *Nature, Lond.*, ii/1933, 446.

Light-destroyed ascorbic acid can be regenerated by H₂S and removing the latter in the trichloroacetic acid filtrate in a way similar to that used by Tillmans, Hirsch and Dick, and Johnson for the regeneration of reversibly oxidised lemon juice.—R. G. Booth and S. K. Kon, *Nature, Lond.*, ii/1934, 536.

The crystalline lens does not contain ascorbic acid although it gives the Tillmans' reaction.—E. I. Evans, *Nature, Lond.*, i/1934, 181.

Estimation of Vitamin C. Vitamin C has to be estimated by the use of guinea-pigs, for rats do not develop scurvy when fed on a diet deficient in vitamin C.

A diet which will produce scurvy in guinea-pigs consists of the following:—

Bran	45%
Split oats	25%
Dried skimmed milk	30%

In addition each guinea-pig is given about 10 drops of a good sample of cod-liver oil twice a week.

The earliest signs of scurvy are seen in certain changes in the structure of the teeth. This can be used for the estimation of vitamin C. The changes have been carefully described by Höjer, (a) *Acta paediatr., Stockh.*, 1924 (suppl.), and (b) *Brit. J. exp. Path.*, 1926, 356. The extent to which the changes may take place in 2 weeks when guinea-pigs are fed on the scorbutic diet plus graded amounts of vitamin C have been described by Key and Elphick (*Biochem. J.*, 1931, 888), who have also described a curve of response to vitamin C in the same paper.

To carry out a test, about 30 young guinea-pigs (300 g. weight) are fed on this diet for 2 weeks. They are divided into, say, five groups of 6 pigs each. Three groups are used for testing three doses of the substance under examination in the ratio 1 : 3 : 9 if no information is available concerning the probable potency of the substance, but in a smaller ratio if the probable potency is known. Two groups of guinea-pigs are used for the standard which must always be tested simultaneously with the substance under examination. Doses of the standard suitable for this test are 0.5 mg. and 1.0 mg. (i.e., 10 units and 20 units). These doses are given daily for 2 weeks. There is no preparatory period of feeding on the diet alone as there is in tests for vitamins A, B and D. At the end of this time, the guinea-pigs are killed, the jaw bones removed, decalcified, and the roots of the incisor examined histologically. (For details of the technique for this, see Goettsch and Key, *Quart. J. Pharm.*, 1928, 168.) The aim of the test is to find one or two doses of the test substances that give approximately the same result as one or two doses respectively of the standard.

Calculations will then give the potency of the substance in terms of international units.

The Estimation of Vitamin C by means of Growth.

Bracewell, Hoyle and Zilva (*Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 146, 1930) have described a method by which the growth of guinea-pigs may be used for estimating vitamin C.

The scorbutic diet consisted of:—

Bran	6 parts by volume
Barley meal	2	„ „
Middlings	3	„ „
Fishmeal	1	„ „
Crushed oats	4	„ „

In addition, 40 to 60 ml. of autoclaved milk made up from a dried powder (i.e., free from vitamin C) was given to each guinea-pig every day. On this diet guinea-pigs of about 300 g. initial weight will succumb to scurvy in 4 to 5 weeks. Groups of about 5 guinea-pigs are given graded doses of the substance under test daily for 90 days. All pigs that die during the test are examined post-mortem and those that have not died during the test are killed at the end of the experiment and also examined for macroscopic signs of scurvy. The results of these examinations taken in conjunction with the growth curves of the animals serve for comparison between the different doses of substance tested. This test should also be carried out with a simultaneous test on one or two doses of the standard.

Occurrence of Vitamin C in Plant Tissues. All fresh vegetables and fruits contain vitamin C, but in varying amounts. Paprika has been found to contain about four times as much vitamin C as the richest lemon juice.

Dried seeds, and seeds soaked just long enough to make them edible, contain no vitamin C but if allowed to germinate for a few days, peas and beans develop vitamin C in substantial amounts.—Fürst, *Z. Hyg. Infektr.*, 1912, 72, 121; Chick and Hume, *Trans. R. Soc. trop. Med. Hyg.*, 1917, 141; Chick and Delf, *Biochem. J.*, 1919, 199; Honeywell and Steenbock, *Amer. J. Physiol.*, 1924, 9, 322.

Lime juice contains only about a quarter as much vitamin C as does lemon juice.

The antiscorvy vitamin in apples.—M. F. Bracewell, E. Hoyle, and S. S. Zilva, *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 146, 1930. Bramley seedlings were found to contain far more vitamin C than any of the other 5 varieties examined.

Samples of lemon juice contained from 0.19 to 0.69 mg. of ascorbic acid per millilitre—L. J. Harris and S. N. Ray, *Biochem. J.*, 1933, 2016.

Figures for the ascorbic acid content of oranges, tangerines and lemon juices.—A. L. Bacharach, P. M. Cook and E. L. Smith, *Biochem. J.*, 1934, 1038.

Antiscorbutic value of oriental fruits and vegetables. As a result of experiments on guinea-pigs, pomelo, cucumber, chico and guava were found to afford the best protection from scurvy.—H. Embrey, *J. trop. Med. (Hyg.)*, 1923, 144.

Orange juice supplied to the Navy has to be tested for vitamin C.—*Pharm. J.*, 1928, 580.

Figures for vitamin C (ascorbic acid) content of 30 foodstuffs determined by means of 2 : 6 dichlorophenolindophenol in milligrammes per gramme.—T. W. Birch, L. J. Harris and S. N. Ray, *Biochem. J.*, 1933, 590.

For an account of the distribution of vitamin C in plant and animal tissues see A. Bessey and C. G. King, *J. biol. Chem.*, 1933, 103, 687.

In animal tissues. The adrenal gland is richer in vitamin C than any other source hitherto investigated, and is three times as active as orange juice or lemon juice.—*Rep. med. Res. Coun., Lond.*, 1931-1932; *Brit. med. J.*, i/1933, 529.

Content in the human pituitary. Result of Szent-Györgyi test in 100 consecutive cases. (The test depends on the strong reducing properties of ascorbic acid: when tissues rich in this substance are brought in contact with a 0.4% solution of silver nitrate for 15 minutes, in the dark, they become blackened from deposit of reduced silver.) The reaction in the anterior lobe was found to be intense in young and middle-aged individuals in whom general bodily nourishment appeared normal; slight or negative in those who had died of long-standing disease with severe emaciation: less intense in the aged than in younger subjects.—J. Gough, *Lancet*, i/1934, 1279.

Figures for the vitamin C content, from observations with 2 : 6 dichlorophenolindophenol, of human tissues show great variation.—M. Yavorsky, P. Almaden and C. G. King, *J. biol. Chem.*, 1934, 106, 525.

Rats and prairie dogs apparently have the power to synthesise this vitamin and naturally never suffer from scurvy. The rat is regarded as not requiring it in its diet.

CLINICAL WORK WITH ASCORBIC ACID

A case of scurvy accompanied by a condition of gastric achylia subsequently to alcoholic gastritis was cured by a daily intravenous injection of 40 mg. ascorbic acid, the diet being kept the same during the time of the injections as it was before.—Schultzer, *Lancet*, ii/1933, 589.

30 mg. ascorbic acid daily given by mouth completely cured infantile scurvy in 2 children in 1 to 2 weeks.—E. Svensgaard, *Lancet*, i/1934, 22.

A mild case in a child 9 months old, successfully treated with ascorbic acid. 20 mg. of ascorbic acid dissolved in 2 fl. oz. of water with milk and malt dextrin was given twice daily for 18 days. Dose then reduced to 10 mg. twice daily for 13 days when symptoms cleared up.—L. G. Parsons, *Proc. Roy. Soc. Med.*, 1933, 36, 1534.

Vitamin C requirement—19 to 27 mg. per os.—G. Göthlin, *Nature, Lond.* ii/1934, 570.

15 to 50 mg. per day of pure ascorbic acid was tolerated by healthy and sick children when they were not able to take adequate quantities of natural fruit juices.—Kramar, *Dtsch. med. Wschr.*, 1933, 1428.

VITAMIN D

Chemistry of Vitamin D. Ergosterol is the particular sterol which becomes antirachitic on irradiation with ultra-violet light. The products of the irradiation can be separated somewhat by heat and fractional condensation. By treating the most active fraction (110° to 125°) (or indeed the original product of irradiation) with 3 : 5-dinitrobenzoyl chloride, two benzoates are prepared which can be separated and reconverted into the corresponding sterols. One of these only has antirachitic properties; it has been named calciferol, the inactive one being named pyrocalciferol.—Askew and co-workers, *Proc. roy. Soc.*, Series B, 1932, 488.

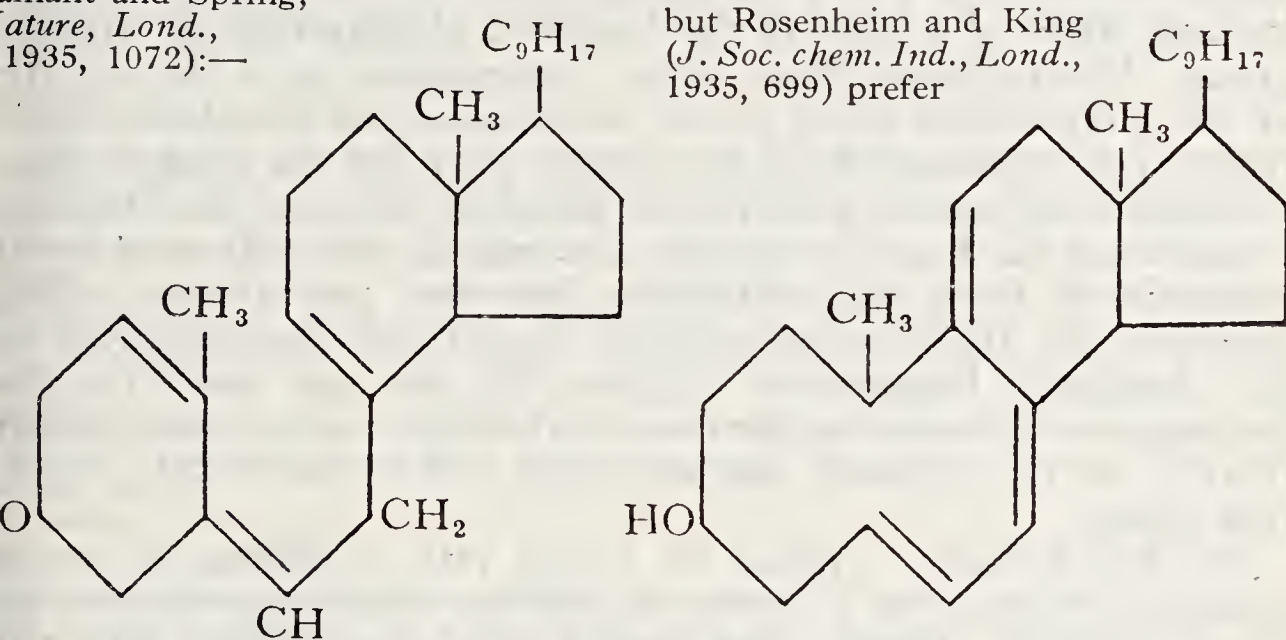
Almost at the same time, German workers isolated vitamin D by somewhat similar methods.—Windaus and Lüttringhaus, *Hoppe-Seyl. Z.*, 1931, 203, 70.

Calciferol. Ergosterol, $C_{28}H_{44}O, H_2O$, of commerce may contain an appreciable amount of dihydroergosterol. The crystalline monohydrate occurs in fine white needles and slowly turns yellow on exposure to air and light. It melts between 162° and 164° with decomposition. The optical activity of a 1% solution in chloroform for sodium light $[\alpha]_D^{20}$, is -125.25° and

mercury green line, $[\alpha]_{5461}^{20^\circ}$, -158.50° (ratio 1.27). Ultra-violet absorption, $E_{1\text{ cm.}}^{1\%}$ 281 $m\mu$, 333. Ergosterol possesses no physiological activity, and is converted by the action of ultra-violet radiation, by a process worked out at the National Institute for Medical Research, into a product from which calciferol, $C_{28}H_{44}O$, (pure vitamin D) can be separated. Calciferol is white when pure and rapidly becomes yellow in contact with oxygen. It melts at about 116° . The optical rotation of a 2% solution in absolute alcohol, $[\alpha]_D^{20^\circ}$, is about -106° or $[\alpha]_{5461}^{20^\circ}$, about $+125^\circ$. Ultra-violet absorption, $E_{1\text{ cm.}}^{1\%}$ 265 $m\mu$, 270 to 485. For a closer analysis of the properties of ergosterol and calciferol see A. L. Bacharach, E. L. Smith and S. G. Stevenson, *Analyst*, 1933, 128.

From tests on bone production in chickens it is concluded that the vitamin D of irradiated ergosterol is different from that of cod-liver oil. Normal bone formation followed the inclusion in the diet of 1% of cod-liver oil, whereas the equivalent of 40% to 120% of this as irradiated ergosterol was required.—J. Steenbock *et al.*, *J. biol. Chem.*, 1930, 97, 249.

Ring Structure of Calciferol. The following has been suggested (Heilbron, *Nature*, *Lond.*, 1935, 1072):—



Reactions of Vitamin D. There are no known reactions specific for vitamin D.

Stability of Vitamin D. The vitamin D of irradiated ergosterol dissolved in olive oil is not heat stable. One sample kept at room temperature for two years lost a large part of its activity. At higher temperatures the loss was more rapid.—Mourdillon, Bruce and Webster, *Biochem. J.*, 1932, 522.

There is no conclusive evidence yet of the stability of vitamin D in cod-liver oil over long periods of time.

Estimation of Vitamin D. The following is an abbreviated account of the method suggested in the *B.P.* '32:—

(a) *Curative.* Select from 3 or 4 litters about 20 young rats ranging in weight from 50 to 60 grammes, and feed for 3 weeks on a rachitogenic diet, e.g.:

Ground yellow maize	33%	or	Ground yellow maize	76%
Whole wheat	.. 33%		Wheat gluten	.. 20%
Wheat gluten	.. 15%		Calcium carbonate	3%
Relatin	.. 15%		Sodium chloride	.. 1%
Calcium carbonate	3%			
Sodium chloride	.. 1%			

Divide the rats into two groups, distributing the rats of each litter as evenly as possible, the rats in one group receiving daily doses of the standard preparation, e.g., 0.25 to 1.0 unit, and those in the other, doses of the preparation being tested. Different rats receive different daily doses, but one rat receives the same dose on each day and the doses are continued for 10 to 14 days. The rats are killed and the extent to which the rickets has been cured estimated by X-rays or by examination of the bones after staining (remove the distal ends of the ulnæ and radii, immerse for 24 hours in 4% *w/v* aqueous solution of formaldehyde, cut in halves by longitudinal section, immerse in 1.5% *w/v* aqueous solution of silver nitrate for a few minutes and expose to light.)

The degree of healing produced by a given dose is not the same in every rat, therefore the average effect of a dose of the preparation being tested in a group of rats should be compared with the average effect of a dose of the Standard Preparation in another group. Where these effects differ, information as to the activity of the preparation being tested, in terms of the Standard Preparation, can be gained from the results, provided the average effect in groups of rats of a series of different doses of the Standard Preparation has been previously determined, the difference being determined from the difference between the average effect produced by the preparation being tested and that produced by the Standard Preparation. When 20 rats are used for the comparison between standard and substance under examination, there is a 1 : 1 chance that the result will be within 20% of the true value.

(b) *Prophylactic*. About 20 young rats, weighing 40 to 50 grammes, from 3 or 4 litters, are fed on a rachitogenic diet for 4 or 5 weeks. During this period they are divided into two groups (as in (a)), one group receiving daily doses of the preparation being tested and the other daily doses of the Standard Preparation in a dose of about 0.1 unit, a given daily dose of either preparation being given to each of not less than 5 rats. At the end of the period the rats are killed and corresponding bones taken from each rat. Moisture and fat are removed from the bones, which are then weighed, incinerated in a crucible, the weight of ash determined, and the percentage of ash in the dry extracted bone calculated. The average percentage of ash in the bones of rats receiving the same doses is then calculated. A dose of the preparation being tested producing the same average percentage of ash as that produced in another group of bones by a known dose of the Standard Preparation is compared in activity with the latter and the activity expressed in units. Where the average percentage of ash in the bones of rats differs between those receiving the preparation being tested and those receiving the Standard Preparation, the test is repeated, using doses of the preparation being tested such as may be judged to produce an average percentage of ash the same as that produced by known doses of the Standard Preparation.

Occurrence. Undoubtedly the richest natural sources of vitamin D are the fish-liver oils. Halibut is often ten times as rich in vitamin D as the best cod-liver oil. Butter is a fair source considering the amount which can be consumed daily. Milk is generally poor in this factor. Green salads probably contain a certain amount of vitamin D while growing and for a short time afterwards, but the amount decreases almost to nothing after keeping a few days under shop or household conditions.

Winter milk and eggs are poorer in this factor than the summer products, which is due partly to the feeding of the cows on green grass in summer and partly to the direct irradiation of the cows with sunlight. The vitamin D potency of winter milk and eggs can, however, be made as great as that of the summer products by giving the cows and hens cod-liver oil or irradiated dried yeast.—*Spec. Rep. Ser. med. Res. Coun., Lond., No. 167, 1932, pp. 87-8.*

Salmon Oil. Probably a more potent antirachitic agent than the average cod-liver oil and compares very favourably in rapidity of action with viosterol. It also provides vitamin A as well as D, together with an easily digested fat.—M. M. Eliot, *J. Amer. med. Ass.*, ii/1932, 1082.

Cacao-nib from Gold Coast cacao has been found to contain 1 unit of antirachitic activity per gramme; a sample of the shell from fermented sun-dried cacao contained 28 units of vitamin D per gramme.—A. W. Knapp and K. H. Coward, *Analyst*, 1934, 474.

Almost any natural product can be activated antirachitically by radiations from a quartz mercury vapour lamp.

Patent rights granted to the Alumni of Wisconsin University for use of ultra-violet light for improving foodstuffs—rights used for the furtherance of research work in the University.—British Patent Specification No. 236,197.

Milk may be rendered highly antirachitic by 16 seconds' exposure to carbon arc rays. Less than 1 quart a day sufficient to protect even negro infants.—A. F. Hess and J. M. Lewis, *J. Amer. med. Ass.*, ii/1932, 653.

Green leaves can be activated antirachitically by irradiation from a quartz mercury vapour lamp—though the vitamin D so formed is soon lost. The feeding of cows on sun-irradiated fresh grass may be the source of the vitamin D content of their milk.—*Spec. Rep. Ser. med. Res. Coun., Lond., No. 167, 1932, p. 87.*

Yeast. The vitamin D potency of sun-irradiated dried yeast.—K. H. Coward, *Lancet*, ii/1933, 920.

Cosmetics containing wool fat. Irradiation of ointments containing wool fat produces vitamin D, and rachitic rats can be cured by inunction with irradiated wool fat. It is improbable that such ointments would have a deleterious effect on health, but a skin cream containing irradiated ergosterol should not be used as a protection from sunburn, since it is a potent therapeutic agent.—C. Moncorps, H. Droller and C. E. Carter, *Münch. med. Wschr.*, 1933, 80, 1289.

Human beings get their vitamin D either from their food or by direct irradiation of their skin and absorption of the vitamin D formed from ergosterol which is present in small quantities in it.

In high latitudes very little ultra-violet light reaches the earth in winter, and practically none reaches those who dwell in smoky towns. Hence, there is every reason why dwellers in Northern towns should suffer from vitamin D deficiency in winter. They cannot make it themselves, and most of the animal fats they get are from animals who have received little ultra-violet irradiation. Margarine firms are taking steps to introduce vitamin D into their products.—A. J. Clark, *Pharm. J.*, ii/1928, 518.

CLINICAL WORK WITH VITAMIN D

Bone formation. Osteomalacia which occurred in field workers in India in spite of their being exposed to strong sunlight yielded to the administration of 4 drachms of sun-irradiated dried brewers' yeast daily for 4 weeks.—D. C. Wilson, *Lancet*, i/1932, 1142.

Remarks on clinical applications of the recent work on bone disease.—E. Mellanby, *Brit. med. J.*, ii/1932, 865.

The incidence of rickets in Manchester.—C. Chisholm, *Brit. J. Child. Dis.*, 1933, 83.

Osteomalacia and diet.—J. Preston Maxwell, *Nutr. Abstr. Rev.*, 1934-5, 1.

Vitamin D probably increases the absorption of phosphates from the food, because "beryllium rickets" can be produced by feeding 0.5% of beryllium carbonate to rats on a normal diet, whereas beryllium phosphate was without effect, the beryllium carbonate making the insoluble phosphate and thus removing the otherwise available phosphorus.—H. D. Kay and B. P. Guyatt, *Nature, Lond.*, i/1933, 468.

The children of the Island of Lewis, in spite of bad domestic conditions, are relatively rickets-free. The explanation is the large use of cod livers and the plentiful use of oatmeal, eggs and fish. Remarkable immunity to rickets of Jews as against Gentiles. Dietary of the former includes much fatty food—oil, eggs and milk.—E. Mellanby, *Lancet*, i/1920, 856. *See also* Roy. Soc. of Med., Discussion, *ibid.*, 604.

Dentition. The influence of vitamin D on the structure of the teeth.—May Mellanby Pt. I. *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 140, 1929; Pt. II, *ibid.*, No. 153, 1930; Interim Report on "The Influence of Diet on Caries in Children's Teeth," *ibid.*, No. 159, 1931; Pt. III, *ibid.*, No. 191, 1934; *Brit. med. J.*, i/1932, 507; ii/1932, 749.

The condition of the teeth of the islanders living on Tristan da Cunha is very nearly perfect. Their diet consists of fish, potatoes, milk, hens' and penguins' eggs and green vegetables. Cereals and sugar are only obtained from ships.—W. E. A. Sampson, *Brit. med. J.*, i/1932, 538.

Vitamin D deficiency, dental caries, and tonsillar enlargement. A clinical investigation of some late effects of rickets.—H. M. M. Mackay, *Lancet*, i/1931, 1230.

General: Vitamin D therapy. Apart from its use in rickets it is the proper remedy for infantile tetany (which is due directly to hypocalcæmia), osteomalacia, celiac disease (as a safeguard against rickets), and it is essential to nursing and expectant mothers, not so much to protect the young as to improve the calcium assimilation of the mother herself and help her to replace the minerals lost to the child or in her milk.—L. J. Harris, *Brit. med. J.*, ii/1933, 371.

The thyroid gland was examined of dogs fed on a diet containing various fats. When fed on butter, cottonseed or linseed oil the thyroid was invariably large, and resembled that of Graves' disease, whereas on a diet of cod-liver oil it was small and histologically normal.—E. Mellanby, *Brit. med. J.*, i/1921, 779.

Hypervitaminosis D is a possibility. The toxic dose of vitamin D is many times the therapeutic dose. With a diet of fresh vegetables, salad and milk, there is less risk of overdosage than with a diet consisting largely of cereals and with a high calcium content.

Small danger of producing D-hypervitaminosis if plenty of milk is given, but real danger with concentrated preparations and insufficient milk and other food.—E. Mellanby, B.M.A. Cent. Meeting, *Brit. med. J.*, ii/1932, 251.

Irradiated Ergosterol. As there is evidence that 10,000 to 20,000 units is on the borderline of toxicity, it would appear safer to fix the maximum therapeutic (curative) dose not higher than 5000 units, which is a suitable maximum curative dose for severe rickets in children of 1 to 2 years. In children of under 18 months (or in milder cases) dosage should be reduced to, say, 3000 units.—L. J. Harris, *Brit. med. J.*, ii/1933, 370.

Irradiated ergosterol given by the mouth in very large doses causes the formation of urinary calculi. It is suggested that this is dependent on an increased absorption of calcium and phosphate from the gut and their excretion by the kidneys.—W. E. Dixon and J. C. Hoyle, *Brit. med. J.*, ii/1928, 883.

A.T. 10, an oil-soluble fraction of irradiated ergosterol (isolated by Holtz and Windhaus), which does not contain vitamin D but has a specific effect on the calcium content of the serum. Taken by the mouth it causes hypercalcæmia in animals and men; effect less rapid than with Parathormone subcutaneously, but more lasting. No considerable increase of blood calcium for first few days after administration, but dose should not be increased as there will be accumulation and dangerous hypercalcæmia, though prolonged use, in correct dosage, is not dangerous.

Small doses orally restore the blood calcium to normal level in the severest cases of tetany, both parathyroprive and idiopathic. Initial dose, 5 to 10 ml. for 3 days, reduced to 1 or 2 ml. daily for 10 to 14 days, then 1 to 2 ml. three

times a week. All other therapeutic measures may be stopped a day or two after beginning of the treatment.—I. Snapper, *Lancet*, i/1934, 729.

This is only available for clinicians working in hospitals, where estimations of serum calcium are carried out regularly (risk of accumulation).

VITAMIN E

Chemistry of Vitamin E. The most active preparation of vitamin E is made by removing the sterols from the unsaponifiable fraction of wheat germ oil and then fractionating the oily residue by distillation under reduced pressure.—Evans, Burr and Althausen, *Mem. Univ. Calif.*, 1927, vol. 8; summarised in *Nature, Lond.*, ii/1928, 136.

The absorption spectrum of wheat germ oil and of many concentrates has been examined but no definite connection between vitamin E and selective absorption has yet emerged.—Morton and Edisbury, *Nature, Lond.*, i/1933, 618.

Absorption at 2940 Å in wheat germ concentrate may be due to "E."—A. J. P. Martin, T. Moore, M. Schmidt, *Nature, Lond.*, i/1934, 214.

Stability of Vitamin E. Wheat germ may be heated to 170° for 3 hours without suffering any loss of vitamin E. Distillation at 220° to 250° *in vacuo* of the most concentrated preparation does not destroy it. Irradiation from a quartz mercury vapour lamp for 45 minutes at 10 in. distance causes partial destruction. Incubation till the oil is rancid causes no loss of vitamin E activity. Aeration for 4 hours at 97° causes no loss. It is stable to alkali at 37° but hot saponification of wheat germ oil causes loss of activity. Hydrogenation causes loss of activity, as also does treatment with acetic anhydride. Acids have no effect on it.—Evans, Burr and Althausen, *Mem. Univ. Calif.*, 1927, vol. 8.

Vitamin E can be reformed from chlorinated and brominated material by boiling with zinc dust and hydrochloric acid in methyl alcoholic solution. The molecule of vitamin E is probably polycyclic and related to the sterols or amyrins. Two oxygen atoms are present in the molecule but only one forms an acetyl derivative. There are probably three reacting double bonds. Active fractions have a well-marked absorption band with maximum at 294 m μ .—Drummond, Singer and Macwalter, *Biochem. J.*, 1935, 456.

Occurrence. Green leaves and embryos of seeds are the richest sources of the vitamin. It is present in small amounts in vegetable oils, in muscle and subcutaneous fats, in milk and butter. Wheat germ oil is perhaps the most convenient form in which the vitamin may be given in concentrated form.

Concentrates of vitamin E have been prepared from lettuce and from wheat germ oil. Chemical and pharmacological properties are described.—H. S. Lcote and H. A. Mattill, *J. biol. Chem.*, 1934, 104, 423.

Therapeutic Use of Vitamin E

A number of cures of sterility in cows were effected by a single intramuscular injection of an ethereal extract of wheat germ. —P. Vøgt-Møller and F. Bay, *et. J.*, 1931, 87, 165.

5 ml. wheat germ oil each day for 2 weeks, then 5 ml. on alternate days for 2 weeks and subsequently 5 ml. every sixth day were given to each of 2 women who had had 4 and 5 consecutive miscarriages respectively; and each one then had a living child born.—P. Vøgt-Møller, *Lancet*, ii/1931, 182.

Doses of 40 drops of wheat-germ oil three times daily for 4 months (third to seventh month of pregnancy) followed by a dessertspoonful of wheat germ three times a day were effective in curing 17 out of 20 cases of habitual abortion.—P. Vøgt-Møller, *Hospitalstidende*, 1933, 76, 621.

36 sheep were given a concentrate of vitamins D, A and E during gestation. Abortion occurred in only 1, whereas of 614 controls not given the concentrate, the incidence of abortion was 13%. There is a 12 to 1 chance that this difference is significant.—Dryerre, *Nature, Lond.*, ii/1933, 751.

THE VITAMIN CONTENT OF SOME COMMON FOOD SUBSTANCES

Substance	Vitamin	International Units per gramme
Cod-liver oil	A	Mostly 1000 to 3000—many outside these limits.
„ „	D	Mostly 100 to 200—many outside these limits.
Butter	A	About 30 to 60—many outside these limits.
„ „	D	About 1, many less.
Boiled cabbage	A	About 10
Halibut-liver oil	A	30,000 to 360,000
„ „	D	2000 to 4000
Wheat germ	B ₁	10
Dried yeast. . . .	B ₁	20 to 40
Orange juice	C	About 20 (variable).
Lemon juice	C	About 20 (variable).
Milk (Jersey, one sample)	A	5
„ (Pasteurised, one sample)	A	3
Milk	D	0·05, often less.
Egg yolk (two samples) . .	D	1·5 and 5·0 respectively

OYSTERS. Contain the vitamins A, B, C, and D, together with a large amount of calcium, phosphorus, magnesium, iodine, zinc, manganese, iron and copper (the latter markedly present owing to feeding on a diatom with high copper content). They possess marked anti-anæmic properties.—L. Binet and M. V. Strumza, *Paris Méd.*, July 1st, 1933, p. 28, per *Brit. med. J. Epit.*, ii/1933, 68.

WATERCRESS.—Remarkably rich in vitamin A; 0·1 g. of green leaf promotes normal growth in rats. Also contains small amount of vitamin D. Growth-promoting properties stronger in spring and summer. Very rich in vitamin C; 1 g. daily protects guinea-pigs for 70 days.—K. H. Coward and P. Eggleton, *Lancet*, i/1928, 98.

In 1929, 100,000 workers were employed in the U.S.A. turning out 10,000 million cans of preserved food. Vitamin content not significantly inferior to fresh foods. As in the course of the canning process the air in the cans is reduced to vanishing point the thermolabile vitamins, which can withstand heat in the absence of oxygen, are little affected by the heating process.—*Brit. med. J.* i/1934, 629.

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Bone marrow changes. Effect of deficiencies of vitamins.—G. M. Findlay *Brit. med. J.*, i/1925, 359.

Following a diet deficient in vitamins or phosphorus, the blood of rats shows a distinct reduction in bactericidal activity to *Staphylococcus aureus*.—G. M. Findlay and I. Maclean, *Biochem. J.*, 1925, 63.

In Greenland, where the natives subsist exclusively on fish and meat, scurvy and rickets are unknown; in Labrador, where civilisation has trained the natives to buy cereals and dried and canned provisions, both diseases are prevalent.—*Lancet*, i/1927, 1358.

The harm done by wrong feeding in the past can never be entirely repaired by belated attention to the need for vitamins, but the use of vitamin-containing foods may prevent the damage from getting worse.—R. H. A. Plimmer, *Practitioner*, i/1926, 232.

Nutrition and child-bearing. The importance of supplying the pregnant woman with a sufficiency of mineral and vitamin factors.—E. Mellanby, *Lancet*, ii/1933, 1131.

Vitamins in relation to the feeding of infants.—E. M. Hume, *Nutr. Abstr. Rev.*, 1932-3, 657.

The vitamins and resistance to infection.—E. C. Robertson, *Medicine*, Baltimore, 1934, 123.

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Vitamins and other Dietary Essentials. W. R. Aykroyd. (Heinemann.)

The Vitamin B Requirement of Man. G. R. Cowgill. (Yale University Press, New Haven, Conn., U.S.A., 1934.)

Nutrition and Disease. Edward Mellanby. (Oliver & Boyd, 1934.)

MILK AND MILK PRODUCTS

MILK ANALYSIS

The importance of milk as an article of diet is reflected in the following pages by the number of Acts, Regulations and Orders by which its production and distribution are controlled, and by the various methods, chemical, physical and bacteriological which are enlisted in its examination. While it is an ideal food when pure, especially for the young and growing, and for *invalids* it is also an excellent medium for the development of organisms both beneficial and harmful, and in the latter case it provides effective means for their distribution throughout a neighbourhood. If, by careless handling, a milk supply becomes contaminated with the germs of disease, it may lay the foundation of future illness in the individual or it may cause and spread an epidemic.

Probably no food has been more subjected to analysis and study than milk and the various products derived from it. It is a very complex fluid containing milk-fat in the form of an emulsion, proteins (casein, albumin, etc.) dissolved or in colloidal suspension, the carbohydrate lactose, and salts of organic and inorganic acids together with minute proportions of many other substances including enzymes and vitamins.

In the accompanying table are mean figures, taken from Leach's *Food Inspection and Analysis*, which show the relative proportions of the main constituents in milk from different sources

	Cow	Human	Goat	Ewe	Mare	Ass
Specific gravity	1.0315	1.03	1.0305	1.0341	1.0347	1.03
Water % . .	87.27	87.41	85.71	80.82	90.78	89.64
Casein % . .	3.02	1.03	3.20	4.97	1.24	0.67
Albumin % . .	0.53	1.26	1.09	1.55	0.75	1.55
Fat % . .	3.64	3.78	4.78	6.86	1.21	1.64
Milk Sugar % . .	4.88	6.21	4.46	4.91	5.67	5.99
Ash % . .	0.71	0.31	0.76	0.89	0.35	0.51

The following figures for the composition of cow's milk are averages quoted by Richmond from 330,000 analyses conducted during 20 years by the Aylesbury Dairy Company. They appear to meet with general acceptance as representing a milk of average good quality.

Water	87.34%
Fat	3.75%
Casein	3.0%
Albumin	0.4%
Sugar	4.7%
Ash	0.75%
Other constituents	0.06%

Higher percentages of fat occur in the milk of certain breeds such as Jersey, Guernsey and other cows.

Standards have been set for the Fat and Solids-not-Fat in milk, which is most readily adulterated by the removal of fat in the form of cream, or by the addition of water. The preliminary analysis of a specimen usually includes determination of the specific gravity, total solids, and fat. Further examination will include the ash, acidity of the sample, proteins (casein and albumin), lactose, etc.; samples should also be examined for preservatives and added colouring matter. The conditions under which a freezing-point determination may be of considerable value are indicated in the following pages.

A sedimentation test is a useful indicator of the cleanliness or otherwise of the methods of production, and in certain cases bacteriological examination of the milk is required.

(1) **Specific Gravity** may be determined by a specific gravity bottle, or a good specific gravity balance. For less accurate purposes a lactometer may be used. The average reading is 1.032 at 60°F. (15.5°C.). N.B.—Low gravity may indicate added water, or in some instances richness in fat.

(2) **Total Solids.** Evaporate 5 grammes of the sample on a water-bath in a tared platinum capsule, dry in the water-oven, and weigh.

Average about 12.8%; minimum 11.5%. Unless the milk is quite fresh it must first be neutralised with decinormal alkali, using a drop of phenolphthalein solution. If decinormal soda is employed 0.0022 g. must be deducted from the weight of the solids for each ml. of soda required.

(3) **Fat.** Many different processes are in use for this important determination, and of these the Werner-Schmidt and Gottlieb methods are convenient for rapid estimations, but a modified Adams extraction method is preferred when greater accuracy is required.

Werner-Schmidt Method. Take 10 ml. of the milk in a 50 ml. tube, graduated in tenths of a ml., and 10 ml. of hydrochloric acid, and boil with shaking until the liquid turns dark brown. Cool rapidly in water and add 30 ml. of ether, shake vigorously and allow to separate. Read off volume of ether, and by means of a pipette transfer 10 ml. to a tared beaker. Evaporate ether, dry at 100°, and weigh. In preference, for accurate work, exhaust the contents of the tube with several quantities of ether and weigh the whole.

Gottlieb Method. 10 ml. of milk is shaken with 1 ml. of 0.96 ammonia, 10 ml. of alcohol and 25 ml. of ether. Light petroleum, 25 ml., is added, the contents of the tube well mixed, and from the clear layer of about 50 ml. an aliquot portion is removed, evaporated and weighed. As in the Werner-Schmidt process it is preferable to draw off the ethereal layer by means of wash-bottle tubes, and repeat the extraction twice more, or until all the fat is removed. Recover the solvent and weigh the residue. Dissolve the fat in light petroleum and deduct the weight of the insoluble matter, if any.—*cf. Analyst*, 1927, 408.

Extraction Process (Adams). 5 ml. of sample is run from a pipette on a strip of "fat-free" filter paper and allowed to dry. This is then rolled up, dried at 100°, and extracted with pure dry ether for 5 hours in a Soxhlet apparatus. The ether is distilled off, and the fat weighed, after drying at 100° for about 20 minutes. There are various modifications of this. Babcock, for example, evaporates with asbestos prior to extraction.

The Gerber Process is a rapid method employed in routine work where several samples have to be examined, any low result suggestive of adulteration being confirmed by one of the more accurate methods given above. The test is carried out in special bottles or tubes known as butyrometers, which are provided with a graduated stem ending in a conical bulb. 10 ml. of sulphuric acid (sp. gr., 1·820 to 1·825) is run into a test-bottle from an automatic pipette, followed by 1 ml. of amyl alcohol, and 11 ml. of the milk, run in carefully down the sides of the bottle to prevent mixing of the three layers. The rubber stopper or special fitting is now inserted, and the contents of the bottle well mixed by shaking and inverting to include the contents of the stem until the whole is dark brown in colour. While still hot it is centrifuged along with other samples, then transferred to a water-bath at about 65° for a few minutes. The volume of fat is now read, the graduations on the flattened stem giving the percentage directly. By moving the stopper slightly the column of fat may be brought into a suitable position for reading.

When the fat and specific gravity at 60° F. have been determined, the total solids may be calculated from the formula

$$T = 0.25G + 1.2F + 0.14$$

where T = total solids; F = fat; and G = excess of gravity over 1·000, or Richmond's Milk Scale based on this formula may be used.

Legally the content must not be less than 3%. *Sale of Milk Regulations 1901 (under Sale of Food and Drugs Act, by Board of Agriculture). Applies to Gt. Britain.*

(With regard to this 3% milk fat standard, it is known that the yield from the same cow may vary greatly, e.g., it may be 2½% in the morning and as high as 4½% in the afternoon.)

Cream in normal milk is about 10%, varying with season, pasture, etc. Milk that has been adulterated with water throws up its cream readily.

(4) **Non-fatty Solids** are determined by subtracting the fat content from the Total Solids. For the purposes of the Sale of Food and Drugs Act they *must not be less than 8·5%*, "or until the contrary is proved it shall be presumed that the milk is not genuine by reason of abstraction therefrom of milk-solids other than milk-fat or by the addition of water."—*Sale of Milk Regulations, 1901.*

Skimmed or Separated Milk. An Amendment in 1912 of the Sale of Milk Regulations replaced the limit, which had been previously 9% total solids, by one of 8·7% **milk solids, other than fat.** This extends to England and Wales.

Taking advantage of the exceedingly low standards laid down by the Board of Agriculture, it appears that milk has been or is toned down with skimmed or separated milk so as to keep the fat content **just within the standard.**

The milk must be labelled (under the Milk and Dairies Act, 1915) "**Machine-Skimmed Milk,**" or "**Skimmed Milk.**"

Although it is "presumed" that a milk is not genuine if it falls below the standard for solids-not-fat, and the onus of proof to the contrary lies upon the vendor, the variations in composition of milk make it desirable that other evidence in confirmation of adulteration should be sought. The quotations below give some indication of the nature and cause of these variations.

Variations in the Composition of Milk—By J. F. Tocher, H.M.S.O., Edinburgh, 1925—quoted by Richmond:—

When the Government figures were laid down, the authorities had no real scientific basis on which to decide what the minimum percentages should be from herds of various sizes, and the present presumptive standards are suitable only in the case of bulked milk

from many cows, i.e., these standards are useful and valid only in the case of bulked milk in large cities.

12% of all samples from individual cows fall below the fat standard and 24% below the solids-not-fat standard.

The percentages of fat and solids-not-fat in a sample of commercial milk depend upon several factors, one of the most important being the number of cows whose mixed milk is represented in the sample. If the sample was, e.g., from 100 cows, one would be quite certain that the milk would be always above the standards.

Cows of three years of age give a higher proportion of solids-not-fat than cows of ten years of age—and the same is true of fat, and the percentages of these constituents vary with the number of weeks the cow has been in milk.

The percentage of lactose falls during the lactation period, but is greater with increased yield of milk. The percentage of albumin rises during the lactation period. If a sample of milk contains a high proportion of lactose, say 5.5%, then the proportion of albumin is low—0.095%, but if lactose is 3.17%, the albumin is 0.15%.

Bulletin No. 16 published by the Ministry of Agriculture and Fisheries in 1932, under the same title, *Variations in the Composition of Milk*, includes the work of several observers, and summarises the position of our knowledge on the subject to that date.

The Sale of Milk Regulations, 1901, provide that a sample of milk that contains less than 3% of fat or less than 8.5% of other solids is to be presumed for the purposes of the Food and Drugs (Adulteration) Act, 1928, not to be genuine until the contrary is proved.

Although these limits are substantially lower than the average percentages of genuine milk, it is recognised that a proportion of genuine milk falls below one or both of the limits. It may be said that the data at present available are insufficient to permit of any exact estimate of this proportion.

That the risk of such a deficiency is appreciable may be gathered from the following experimental evidence. This is given in the form of a table of results obtained by Cranfield between 1923 and 1926 at the Midland Agricultural College from the analysis of weekly samples of the milk of 15 herds. The samples were taken from the mixed milk of the whole herd in each case, the herds including as large a variety in size, etc., as possible.

Of the 730 samples of mixed milk 59, or 8.1%, contained less than 3% of fat; and of 518 samples of milk 60, or 11.6%, contained less than 8.5% of solids-not-fat.

Tocher found that of 626 samples of milk of individual cows 6, or 0.96%, contained less than 3% of fat, and 167, or 26.7%, contained less than 8.5% of solids-not-fat.

Other figures quoted include analyses of milk taken from churns

delivered to two dairy companies over a period of one year. From these it is concluded that 7% to 8% is a maximum figure for the percentage of total churn samples likely to be found deficient in fat, and 5% a similar maximum figure in the case of non-fat solids, for milks sold by dairy farmers of this class.

The individuality of cows is referred to as a circumstance affecting the composition of milk.

An extreme case is given of a cow which appeared healthy and normal in every other respect. Out of 133 samples of the milk of this cow between 1924 and 1925 only one exceeded 8.5% in solids-not-fat. 26 samples were below 8% and 10 below 7% the lowest percentage recorded being 5.3.

"It is often said that although the milk of a particular cow may, owing to her individuality, fall below the limits mentioned in the Sale of Milk Regulations, the mixed milk of a herd of cows does not usually vary very much in composition from the average." There is some truth in this, but it requires considerable qualification.

In the first place there are many small herds, and in the second place it is very seldom that all the milk of a large herd is thoroughly mixed. Some dairy companies and producers pour the whole of the milk into one vessel but the usual practice is to pour the milk of each individual cow through a cooler into a churn, and in this case it is only the milk of the number of cows necessary to fill the churn—say seven or eight—which is mixed.

From observations on the intervals between successive milking it is stated that the results are sufficient to confirm the commonly accepted opinion that it is not unlikely that the fat in any milk will be found to fall below the 3% limit when a long interval has elapsed since the previous milking.

No well-marked variations in the percentage of solids-not-fat appear to occur in connection with intervals of milking, but

"So far as the percentage of fat is concerned the interval between milkings constitute the most important of the known factors associated with variations in the composition of milk."

Other causes of variation discussed are age, breed, period of lactation, influence of food, abnormal conditions etc., and the possible effect of employing relatively unskilled milkers is not overlooked.

The extent to which milk varies in composition from day to day or within short periods, is of great importance in connection with the practice of taking "appeal" samples at farms in order to ascertain whether the original sample was adulterated or naturally poor in quality. There is sufficient evidence to show that the variations are considerable.

In the case of a cow which appeared to be in excellent health the fat in the evening milk rose from 3.1% on 18th April to 6.6% on the 19th April, and fell from 7.0% on 22nd May to 2.5% on 23rd May. The fat in the morning's milk rose from 2.1% on

th May to 5.9% on 9th May, and fell the next day to 2.9%. The solids-not-fat fell from 8.75% on 18th April to 7.85% on 9th April, and rose from 7.5% on 28th April to 9.05% on 29th April.

Apthous Fever. (*Foot and Mouth Disease.*) The milk in this disease presents difficulty to the analyst. It presents different appearances in different cases; in those where there are ulcers on the teat, either externally or just inside, the pus from these ulcers mixes with the milk, and a high fatty residue, from which cholesterin, nuclein, lecithin, and milk fat may be separated, results. If, on the other hand, there are no ulcers, and no affection of the udder, the milk in the more severe cases may be deficient in solids, and especially in milk fat, or does it recover its normal composition until about the seventh or eighth day, when the cow begins to improve.—Winter Blyth.

(5) **Lactose (Milk Sugar).** *Average content 4.4%.*

The percentage content falls during the lactation period, but is greater with increased yield of milk.

The sugar can be determined by a volumetric or gravimetric estimation of its copper-reducing power after removal of proteins and fat. For gravimetric purposes this is best effected by diluting 5 ml. of the milk to about 400 ml. in a 500 ml. graduated flask and adding 10 ml. of Fehling's No. 1 copper solution and 35 ml. of N/10 sodium hydroxide. After shaking thoroughly and adjusting to the mark the liquid is filtered through a dry paper, 10 ml. of the filtrate being used for the determination. For a volumetric process with Fehling's solution see the method of Lane and Eynon under Condensed Milk. It is not necessary to clarify the milk, and the process is quick and accurate.

Another convenient and rapid process is that of H. D. Richmond (*Analyst*, 1925, 17). 10 g. of milk are weighed into a 100 ml. graduated flask, diluted with 50 ml. of distilled water and 10 ml. of Mayer's reagent and 2 ml. of N/1 sulphuric acid added. The whole is well shaken, diluted to 100 ml. and filtered. After neutralising 25 ml. of the filtrate to phenolphthalein (1 drop used), 20 ml. of N/10 iodine solution and 30 ml. of N/10 caustic soda solution are added. The mixture is allowed to stand for 10 minutes and after the addition of 4 ml. of N/1 sulphuric acid the excess of iodine is titrated with N/10 sodium thiosulphate.

Percentage of lactose ($C_{12}H_{22}O_{11}, H_2O$)

$$= \text{ml. N/10 iodine used} \times 0.072 \times \frac{100 - (0.3 + \text{fat} \times 1.1)}{\text{wt. of milk taken.}}$$

Lactose Determination by Polarimeter—

Add to 60 ml. of the milk 10 ml. of a solution of mercury in twice its weight of nitric acid (sp. gr. 1.43) diluted with four times its volume of water. Make volume up to 102.4 ml., filter. Note rotation in 200 mm. tube,—divide by 2 and by 53 the specific rotation for lactose. Result is the amount of lactose per ml. in the solution. Multiply by 100 to give the amount in 60 ml. of milk.

(6) **Casein Estimation.** *Average content 3.2%.* Dilute 10 ml. of the sample with 300 ml. of water, and add strong acetic acid drop by drop to complete precipitation. Pass in carbon dioxide for 20 minutes, collect the casein and fat on a weighed filter paper; wash thoroughly first with alcohol, then with ether to

remove fat (well conducted in a Soxhlet thimble on water-bath) dry and weigh.

Many proteins are precipitated by acetone. Weyl applied this property to estimation of the proteins in cow's milk and in fresh bullock's blood and obtained concordant results. The milk or blood is diluted with an equal volume of water and poured into four volumes of acetone. The precipitate is collected, washed with equal volumes of acetone and water, then with alcohol, and is finally extracted with ether in a Soxhlet apparatus, dried and weighed.

Colostrum. The milk from mammals shortly after birth of their young differs from normal milk in containing a very high percentage of an albumin closely resembling blood albumin. The proteins it contains are soluble. Colostrum provides readily absorbable nutriment, as the infant's stomach contains no gastric juice at the commencement. It is highly laxative in properties.

The following analyses by Engling show the composition of colostrum from a cow 8 years old:—

Time after Calving	Specific Gravity	Fat	Casein	Albumin	Sugar	Ash	Total Solids
Immediately	1.068	3.54	2.65	16.56	3.00	1.18	26.93
After 10 hours	1.046	4.66	4.28	9.32	1.42	1.55	21.23
„ 24 „	1.043	4.75	4.50	6.25	2.85	1.02	19.37
„ 48 „	1.042	4.21	3.25	2.31	3.46	0.96	14.19
„ 72 „	1.035	4.08	3.33	1.03	4.10	0.82	13.36

The average of 22 analyses by Engling, of colostrum from different cows showed total solids 28.31, fat 3.37, casein 4.83, albumin 15.85, sugar 2.48, ash 1.78.—Leach, "Food Inspection and Analysis." See also *Analyst* 1913, 107, for the results of analysis of colostrum from 20 different cows, in which the fat ranged from 1.3% to 9.0%.

Cow's milk contains about twice as much **phosphatide** as human milk, the amount being higher with a milk or cream with a high percentage of fat, though there is no parallelism between the fat and phosphatide content. Milks containing a considerable amount of colostrum also show a high phosphatide content. The total phosphorus of cow's milk averages about four times that in woman's milk, and is still higher in goat's milk.—*J. Amer. med. Ass.*, ii/1925, 775.

The proteins of milk consist almost entirely of casein and albumin. Analyses show mean ratios as follows:—

	Casein	Albumin ("Lactalbumin")	Maximum	Minimum
Cow's milk	6	1	7 to 1	4.5 to 1
Goat's „	3	1	3 to 1	2 to 1
Sheep's „	3	1	4 to 1	3 to 1
Mare's „	1.5	1		
Ass's „	1	2.3		
Human „	1	1		

The proportion of these two forms of protein is adjusted to the needs of the animal, the albumin being easily digested, and the casein digested with difficulty. A 16 lb. infant requires more casein than one weighing 12 lb. though of the same age, and the human milk changes accordingly. More and more casein and less and less albumin is required by the child as time goes on.

The milk supplied in this country in a large proportion of cases is from cows in calf. That from cows not in calf is more digestible, as the drain of the embryonic calf interferes with quality of the pregnant cow's milk.

Lecithin contained in various milks. Human, average, 0.0499%, cow's 0.0629%, ass's 0.0165%.

(7) Albumin Estimation. *Average content 0.4%.*

Various methods are used. The following of Ritthausen (mentioned by Blyth) is simple. Dilute 10 g. of milk with 90 ml. of water at 42°. Add 1.5 ml. of 10% acetic acid. Casein settles in 5 minutes. Albumin remains in solution. The precipitated casein is treated with alcohol and ether and may be weighed. Neutralise the filtrate with NaOH, add 3 ml. of 10% acetic acid, boil 15 minutes and collect on a filter, or a Kjeldahl may be conducted, multiplying the N by 6.38. Diminished content below 0.41% to 0.45% may be useful to show adulteration.—See Blyth, p. 250.

Mineral Matter of milk can be obtained by igniting the milk solids. If the milk has been neutralised before evaporation, deduct 0.0053 g. for each ml. of N/10 soda added.

N.B.—A dilution of normal milk with water will reduce the ash almost proportionately to quantity of water added, so the combination of a low ash and low non-fatty solids point strongly to addition of water.

The Salts in human and cow's milk vary very greatly. Nearly one-third of the salts of cow's milk are alkali citrates and alkali earth citrates. Human milk contains 0.5 g. of citric acid as citrates, whilst cow's milk contains from 1 to 1.5 g. per litre.

The Freezing-point of Milk

Owing to the fact that the freezing-point of milk shows very slight variation, much attention has been paid to its determination as a means of detecting added water, and of late years there have frequently been prosecutions under the Food Acts in which the freezing-point of the samples formed an important part of the evidence of adulteration put forward.

There are differences of opinion as to the advisability of resting convictions on the results of freezing-point determinations (Tocher: see *Times*, Sept. 12, 1934, report of B.A. meeting, and *Pharm. J.*, ii/1934, 314), but there can be no doubt that the method is of great value *in certain cases* when taken in conjunction with chemical analysis which will, of course, always be the case in practice.

In large towns and cities, where the supply consists of mixed milk from a very large number of herds, the fat and non-fatty solids do not fall below the standards laid down by the Board of Agriculture, unless the milk has been tampered with, but the milk from a small herd, or more particularly from individual cows, may be abnormal and yield lower figures than 3% for fat and 3.5% for non-fatty solids. In such a case it is claimed that a freezing-point determination will distinguish between milk which has been watered and abnormal milk, and that where an "Appeal to the Cow" sample is available, the comparisons based on chemical analysis are confirmed by the findings dependent on freezing-point determinations.

In a Report to the Local Government Board in 1914 Dr. Monier-Williams reviewed the work done in previous years, and gave the results of many experiments carried out by him in an apparatus which he had devised. He obtained an average freezing-

point of -0.5345° , the values found ranging from -0.558° to -0.514° .

He concludes that the freezing-point appears to be the most constant of any of the properties exhibited by genuine milk. It is unaffected by the removal of fat, or by the addition of separated milk, but it is raised by the addition of water.

"The method may, in certain circumstances, be applied with advantage, as a confirmatory test, to the detection of added water, and to the approximate estimation of the amount present.

"Owing, however, to the experimental difficulties involved in obtaining reliable results, it is somewhat doubtful whether the method is capable of general application for purposes of milk control."

Dr. Monier-Williams' experiments were carried out under conditions ensuring scientific accuracy, and the values quoted in his report had been subjected to all necessary corrections.

Since that time an apparatus devised by Hortvet has come into use among analysts. Its description and use are given in "Methods of Analysis" (A.O.A.C.).

Cooling is produced by the evaporation of ether as in the Monier-Williams apparatus, the process being more readily controlled than when mixtures of ice and salt are employed. Determinations are made under standard conditions, and no corrections are made for sources of error. The depressions found are probably a little too high, but are strictly comparable with one another. (Elsdon, in *Recent Advances in Analytical Chemistry*, Vol. I, p. 252.)

Elsdon and Stubbs (*Analyst*, 1930, 423) make the following suggestions: "that an average of 0.54° may be taken for the purpose of calculating added water, but that no milk should be considered watered on the evidence of the freezing-point of a single sample alone, unless the depression falls below 0.53° ."

These authors also point out that as a milk becomes sour the depression of the freezing-point increases, so that the method is only applicable to fresh milk or to slightly sour milk after suitable correction.

A number of instances of adulterated samples are given, in some of which the solids-not-fat are near or well above the 8.5 limit, but which are shown by the evidence of the freezing-point to be watered. This is confirmed in every case by the comparison samples taken from the farm, as will be seen from the example quoted here from a table given in the paper.

cf. Report by Monier-Williams.

It will be observed that writers sometimes refer to the freezing-point of milk, and sometimes to the depression of the freezing-point, which is apt to be confusing, especially when the terms "higher" and "lower" are employed. A freezing-point of -0.520° is obviously higher than one of -0.550° .

But in the depression, Δ , of the freezing-point with reference to water, 0.550 would be higher, i.e., a greater depression than 0.520 .

This mode of expression has the advantage that the terms higher and lower correspond with the actual figures, and the constant repetition of the minus sign is avoided.

Original		Comparison	
Solids-not-fat	Freezing-point	Solids-not-fat	Freezing-point
%	°C	%	°C
7.6	—0.464	9.1	—0.553
8.6	—0.524	8.6	—0.540
8.8	—0.521	9.1	—0.542
8.5	—0.518	8.9	—0.543
8.4	—0.498	8.7	—0.542
8.4	—0.510	8.7	—0.543
8.7	—0.526	8.6	—0.543

The original table also contains acidity figures showing that the samples were fresh in each case; and the number of cows whose mixed milk is represented in the sample is given for each farm.

That the evidence furnished by the freezing-point determination is sometimes in favour of the vendor is illustrated by the following interesting case, for which we are indebted to the report of the Lancashire County Analyst. A sample contained 4.4% of fat, and 8.25% of solids-not-fat, but a normal freezing-point of —0.538°. Two "appeal" samples contained 3.8% and 4.2% of fat and 8.6% and 8.4% of solids-not-fat respectively, with a freezing-point in each case of —0.538°, confirming the opinion that the original milk was genuine.

Monier-Williams, in a paper (*Analyst*, 1933, 245) on the determination of the true freezing-point of milk, states that the apparatus used by him in 1914 was too elaborate for routine work. It was extensively modified and standardised by Hortvet (*J. Ind. Engng Chem.*, 1921, 13, 198) whose "cryoscope" was officially adopted by the Association of Official Agricultural Chemists in the United States.

"The **Hortvet Cryoscope** is a standardised apparatus, and gives results which, while they do not purport to represent accurately the true freezing-point of milk, i.e. the temperature at which milk is in exact equilibrium with ice, are yet strictly comparable and reproducible with a fair degree of precision. The same thing may be said, more or less, of several other forms of apparatus which have been adopted officially or semi-officially in other countries (Holland, Germany, New Zealand, etc.)."

Monier-Williams proceeds to describe the new apparatus which he has designed for quick and accurate determination of the true freezing-point, the only correction required being for super-cooling. He gives the following comparative results obtained with the two instruments.

The freezing-points of three different samples of milk taken with the Hortvet Apparatus were:—

—0.535°, —0.534°, and —0.534°.

The thermometer used was now transferred to the Monier-Williams apparatus, and the following figures obtained after correction for super-cooling:—

—0.522°, —0.520° and —0.519°.

It has been recommended by the Council of the Society of Public Analysts (*Analyst*, 1933, 58):

- (1) that for administrative purposes the freezing-point of samples of milk should be determined in accordance with the Hortvet technique exactly as described in *Official and Tentative Methods of Analysis of the A.O.A.C.*, 3rd Edn., 1930.

No correction other than those directed therein should be applied.

- (2) That the freezing-points thus obtained should be recorded, for example, as

Freezing-point (Hortvet) —0.550°.

With reference to the *employment of the method in other countries* R. L. Andrew (*Analyst*, 1929, 210) describes the practice in the New Zealand Dominion Laboratory, where a simple form of Beckmann's freezing-point apparatus is used. He concludes (after 17 years' experience) that genuine milk has a freezing-point, determined by this method, of not higher than -0.550° . If the freezing-point rises to -0.520° the milk has certainly been adulterated with about 5% of added water. A series of instructive examples is given of the application of the method to the detection of added water, or of abnormality at the source of supply. The real value of the test, it is claimed, is shown in the improvement brought about in the milk supply of Wellington City.

A. van Raalte states (*Analyst*, May, 1929) that the method has been used in Holland since 1898.

A. J. Parker and L. S. Spackman (Auckland, New Zealand) contribute a paper entitled "Investigations on the Relations between the Acidity and Freezing-Point of Milk." (*Analyst*, 1929, 217).

Results with milks containing added water tend to show that when the cryoscopic method is used for the determination of added water in milk it can be applied with accuracy only when the samples are quite fresh.

Added Water.—A table is given in the A.O.A.C. *Methods of Analysis* for the percentage of added water corresponding to the determined freezing-point depression.

The percentage of added water (W) may also be calculated as follows:—

$$W = \frac{100(T - T')}{T}, \text{ where}$$

T = the average freezing-point of normal milk (-0.550°), and T' = the observed freezing-point of a given sample.

In the ordinary analysis of milk the amount of water added is obtained from the solids-not-fat figure by an exactly similar formula.

$$W = \frac{100(S - S')}{S}, \text{ in which}$$

$S = 8.5$ (the standard laid down by the Board of Agriculture)

S' = the solids-not-fat determined in the given sample.

As 8.5 is an arbitrary minimum figure the amount of added water so calculated will not as a rule agree closely with that given by the freezing-point formula. It is only correct if the original milk contained 8.5% of solids-not-fat.

Recent work published includes the examination of 1000 milk samples by the Hortvet freezing-point process, by J. R. Stubbs and G. D. Elsdon (*Analyst*, 1934, 146). The results show an average freezing-point depression, Δ , of 0.544° with extremes of 0.529° and 0.563° . All the samples were believed to be genuine.

"No material difference has been found between morning and evening milks or between milks produced in different months of the year, and no apparent correlation has been found between the freezing-point depression and the amount of solids-not-fat present."

In explanation of the last point, the authors state that the freezing-point depends on the osmotic pressure of the blood of the cow, and not on the total amount of solids in solution in the milk. The solids-not-fat may be low owing to a deficiency in lactose, and the effect on the freezing-point, but not on the solids-not-fat, may be counterbalanced by a small amount of mineral salts.

See also page 585 of the same volume, where Elsdon and Stubbs point to the results obtained by workers in different laboratories as evidence that the freezing-point test for the detection of the addition of water to milk is highly satisfactory, and that its indications may safely be accepted. Results are given for samples of the same milk using the Hortvet and Monier-Williams cryoscopes and Hortvet results obtained by different observers on the same sample.

4 *Résumé of Various Acts of Parliament, Regulations, and Official Publications*

MILK AND DAIRIES (CONSOLIDATION) ACT, 1915. (*Does not extend to Scotland or Ireland*). Came into operation September 1st, 1925.

Section 1. Gives the Local Government Board powers to make Orders for Registration of Dairymen, Inspection of Cattle, Dairies, and Milk Stores, for the use of the designation "Certified Milk," and allied matters.

Section 3. Gives M.O.H. power to stop the supply of milk from a dairy which has caused, or is likely to cause, tuberculosis.

Section 4. Requires the local M.O.H. to trace the source of supply of tuberculous milk, and to give notice to the County M.O.H., who shall then cause the cattle in question to be inspected.

Section 5. Any person selling or allowing to be sold, or using or allowing to be used in the manufacture of products for human consumption the milk from any cow which has given tuberculous milk, or is suffering from emaciation due to tuberculosis, or inflammation of the udder, or diseases specified (acute mastitis, actinomycosis of the udder, anthrax, foot and mouth disease, and suppurative of udder) is guilty of an offence under the Act, if he had previously received notice, or otherwise knew, or with ordinary care should have ascertained, that the cow was giving tuberculous milk.

Section 8. Allows L.G.B. Inspectors, M.O.H.s, etc., to take for examination samples of milk at any time.

Section 10. A local authority *may* appoint one or more veterinary inspectors for the purposes of the Act, and *may* provide or arrange for facilities for bacteriological or other examinations.

Section 12. Allows sanitary authorities to maintain depots for the sale of milk at not less than cost price, specially prepared for consumption by infants under 2 years, and to provide laboratories, plant, etc.

(*It would appear therefore that the onus of carrying out the provisions of the Act falls on the shoulders of the local M.O.H. There is no provision in the above sections for routine periodic inspections.*)

MILK AND DAIRIES ORDER, 1926, made under the Milk and Dairies (Consol.) Act, 1915. Came into operation October 1st, 1926.

S. R. & O., 1926, NO. 821.

Section 1 et seq.—Refers to Registration of Dairies, Cowsheds, etc.

ART IV.—*Health and inspection of cattle.*

Section 8. Every county and county borough council shall cause such inspections of cattle to be made as may be necessary and proper for the purposes of the Act.

Section 11. Veterinary Inspectors to serve a notice stopping supply of milk from cows suffering from: any comatose condition, any septic condition of the uterus, any infection of the udder or teats likely to convey disease in addition to the diseases specified in Section 5 of the Act. (*q.v.*)

ART V.—*Provisions for securing cleanliness of dairies and protecting milk against infection.*

Sections 17, 18, 19. Prevent the sale of milk by persons suffering from, or from premises where there are persons suffering from, infectious disease.

(NOTE.—*Inspections are only to be carried out "when necessary for the purposes of the Act," i.e., after tuberculous milk has been found exposed for sale.*)

MILK AND DAIRIES (AMENDMENT) ACT, 1922. Came into operation September 1st, 1922.

This Act postponed for a further period the Milk and Dairies (Consol.) Act, 1915.

2. Gives local authorities power to refuse registration of, or remove from register, retailers of milk likely to endanger the public health.

5. No person shall sell or offer or expose for sale the milk of a cow suffering from tuberculosis of the udder, and in the event of his so doing he shall be liable to a fine on first offence of £20, and for second and subsequent offences a fine of £100 or 6 months' imprisonment or both.

(NOTE.—*Section 5 of this Act places the responsibility on the purveyor of the milk.*)

MILK (SPECIAL DESIGNATIONS) ORDER, 1923, made under the 1922 Amendment Act. Came into operation July 1st, 1923.

S. R. & O., 1923, NO. 601.

3. The special designations under which milk may be sold are: (1) "**Certified**"; (2) "**Grade A (Tuberculin Tested)**"; (3) "**Grade A**" and ("**Pasteurised**."

6. In the case of "Certified" or "Grade A (Tuberculin Tested)" milks the producer must possess a vet's. certificate showing the results of an examination carried out *not more than three months before* and a certificate of a prescribed Tuberculin Test carried out within a similar period, and in the case of "Grade A" milk a vet's. certificate of examination of milch cows carried out *not more than one month before*. Licences to be renewed yearly.

THIRD SCHEDULE.

PART I. Conditions subject to which licences for selling milk as "**Certified**" are granted.

Producers to have every animal examined and submitted to a T.T. every 6 months. No animal which has not passed the T.T. shall be added to the herd. Animals reacting to be removed from the herd. Complete register of animals to be kept. The herd to be completely isolated from all other cattle.

The milk must be bottled on the farm immediately after production.

PART II. Provides the conditions subject to which licences for selling milk as "**Grade A (T.T.)**" are granted.

The milk shall not at any stage be treated by heat.

PART III. Conditions, etc., for selling milk as "**Grade A**."

No reacting animal shall be in the herd. Milch cows to be examined every 3 months. Diseased animals to be removed from the herd immediately. If tubercle bacillus is found in the milk the producer shall remove diseased animals from the herd and inform the licensing authority how the animals have been disposed of. Complete register of cows to be kept and cows in milk in the herd to be kept separate from all other cows in milk.

The milk is not to be treated by heat at any stage, unless a licence to sell such milk as Pasteurised has been granted.

DESIGNATED MILKS

Grade A milk is superior to the ordinary milk of the country, and reasonably safe.

The Tuberculin Test is to be done at 6-monthly intervals. Reactors are to be removed forthwith. Combined subcutaneous and ophthalmic tests of cows are required in respect of herds supplying tubercle-free milk.—*Brit. med. J.* i/1925, 409. (*Vide Intradermal Test infra for latest recommendation.*)

Certified Milk (the highest grade) is produced under similar conditions to the above, but is to be bottled on the farm immediately after production.

The cap is to bear name and address of producer, date, and the words "**Certified Milk**."

Results show that it is possible to maintain the Ministry's standard for certified milk, and that clean milk production rests not so much on building and equipment as on the skill of the workers and the interest of the farmer or milk dealer.—R. S. Williams, *Brit. med. J.*, ii/1926, 242.

Pasteurised Milk under the Order must be submitted to a temperature of not less than 145° or more than 150° F. for at least $\frac{1}{2}$ hour and immediately cooled to 55° F. or lower. "Flash" methods are not allowed.

Bacteriological Standards

CERTIFIED. 30,000 maximum bacteria per ml., and no coliform bacillus in 0.1 ml.

GRADE A (TUBERCULIN TESTED) and GRADE A. 200,000 maximum bacteria per ml., and no coliform bacillus in 0.01 ml.

GRADE A MILK PASTEURISED. Not more than 30,000 bacteria per ml., and no coliform bacillus in 0.1 ml.

PASTEURISED. Not more than 100,000 bacteria per ml.

Technique in Grading Milk

Precise instructions to ensure uniform laboratory methods are given in Circular issued by the Ministry of Health. See page 422.

Prices of Designated Milks

	Winter Prices		1934	Summer Prices	
	Quart	Pint		Quart	Pint
Certified Milk	1/1½	8d.		1/1½	8d.
Grade A (tuberculin tested) milk ...	9d.	4½d.		8d.	4d.
Grade A milk, pasteurised	9d.	4½d.		8d.	4d.
Pasteurised milk	7d.	3½d.		6d.	3d.

Milk is now obtainable in sterilised paraffin-waxed sealed cartons at the ordinary prices for household milk.

MILK AND DAIRIES (SCOTLAND) ACT, 1914. *Came into operation September 1st, 1925.*

3. Every local authority may appoint a qualified Veterinary Surgeon to act as an inspector under the Act, and may make arrangements for the bacteriological or other examinations of samples.

4. The M.O.H. or Sanitary Inspector shall inspect every dairy in the district at least once a year, and the Veterinary Inspector shall inspect the cattle at least once a year, and these authorities have power to examine cattle and dairies in other districts consigning to their own district contaminated or impure milk.

5. The local authority has power to authorise inspection of premises or examination of cattle of occupiers, not dairymen, who sell milk in small quantities to employees or neighbours.

7. It is unlawful for a person to trade as a dairyman without a certificate of registration from the local authority.

9. It is the duty of every local authority to make by-laws:—(1) for inspection of cattle in dairies; (2) for prescribing the structure and cleansing facilities of dairies; (3) for the prevention of impurities in milk; (4) for prescribing precautions against infection or contamination of milk.

10. The Local Government Board may require enforcement of the Act by local authorities.

11. If a local authority believes that another district consigning milk to its own is not carrying out the provisions of the Act it may complain to the L.G.B.

12. The Board may make Orders concerning measures for cooling milk and protecting it against infection or contamination, for the prohibition of colouring matter or addition of other substances, for the manner of conveyance of the milk, and for the labelling of receptacles.

13. **No person shall sell milk from a tuberculous cow** or from a cow suffering from infectious disease.

14. Dairymen must give notice to the authority of any tuberculous or infected cows, or (15) of any infectious disease of persons on the premises, and (17) persons so infected must not assist in the dairy.

20. Where there is an outbreak, or a liability of an outbreak, of infectious disease, or where milk supplied is contaminated or impure, the local authority may require the dairyman, whether within or without the district, to give a complete list of the names and addresses of all his customers and of the sources from which he obtained the milk.

21. Authorities shall have power to take samples of milk.

22. A Veterinary Inspector may apply to any cow in any district the Tuberculin or other test to discover whether a cow has tuberculosis.

27. A warranty or invoice shall not be available as defence in respect of milk.

28. Local authorities may establish depots for sale of milk for consumption by infants under 2 years.

Milk (Special Designations) Order Scotland, 1923.—S. R. & O., 1923, NO. 656/s.42, and the **Milk (Special Designations) Amendment Order Scotland, 1923.**—S. R. & O., 1923, NO. 869/s.55.

These Orders have essentially the same objects as the Order for England and Wales. They are issued by the Scottish Board of Health.

THE TUBERCULOSIS ORDER, 1925. *Came into operation September 1, 1925.*

S. R. & O., 1925, NO. 681.

Sections 2, 10, 11. Any person having a cow which appears to be suffering from tuberculosis of the udder or any chronic disease of the udder, or from tuberculous emaciation, or from chronic cough, and showing definite clinical signs of tuberculosis must immediately give information to a police-constable or an inspector, and must isolate the animal and keep the milk separate.

Section 4. A Veterinary Inspector may enter at any time and examine animals and require any cow to be milked and take samples of milk.

Section 5. Where the Inspector's report shows the animal to be suffering from tuberculosis, the local authority must immediately notify the owner and slaughter the animal.

(REMARKS:—*If the Ministry of Health enforced all the above Rules and Regulations more vigorously, it would undoubtedly lead to a considerable reduction in bovine tuberculosis, but the weakness of the whole of the legislation seems to be concerned with the work of the Inspectors.*)

Tuberculin Tests in Cattle with special reference to the Intradermal Test.

MEDICAL RESEARCH COUNCIL. SPECIAL REPORT SERIES, No. 9. H.M.S.O., 1925.

The **subcutaneous test** is satisfactory under laboratory conditions, but not under farm conditions. The **intradermal test** is superior, while the **ophthalmic test** must be regarded as a subsidiary test. The percentage of error with the intradermal test is small; animals diagnosed as tuberculous by this test have not shown tuberculosis on naked-eye examination *post mortem*, but have been proved tuberculous by microscopic examination and guinea-pig inoculation. The test has the advantages over the subcutaneous test that temperature observations are not required, that the animal need not be kept at rest, that it does not interfere with farm routine, that only three observations are usually necessary, that a smaller quantity of tuberculin is needed, and that the technique is easily acquired. "**Old tuberculin**" (either bovine or human strain) is used; it must be of proved high potency and is given undiluted. In combining the ophthalmic test with the intradermal test frequent examinations of the animal's eyes are necessary since the reaction when positive is apparent 24 hours after the second instillation.

Modified Intradermal Test. A further report "The Intradermal Tuberculin Test in Cattle" (J. B. Buxton and A. S. McNalty, *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 122, 1928) by the Tuberculin Committee of the M.R.C. states that the intradermal test is more trustworthy. It involves two injections of tuberculin—a "**sensitising**" and a "**reacting**" dose—on different occasions. Can be readily performed under farm conditions, has little or no effect on milk yield and is free from risk in pregnant cows and young animals. Ophthalmic test unreliable.—*Brit. med. J.*, ii/1928, 808.

The following table relating to England and Wales summarises the position (to 1933) in counties and in such boroughs as have administrative powers under the Diseases of Animals Acts:—

Areas	Staff	Cow and Heifer Population
(i) Routine Inspection by whole-time Veterinary Officers		
6 Counties*... ..	26	311,617
25 Boroughs	38	27,920
(ii) Routine Inspection by part-time Veterinary Officers		
8 Counties	64	237,588
85 Boroughs	94	30,044
(iii) No Routine Inspections		
45 Counties	—	2,073,137
84 Boroughs	—	27,448

* Cumberland, Durham, Middlesex, Surrey, Yorkshire (North Riding) and Yorkshire (West Riding).

The county of Nottingham, where a dual system of clinical inspection and herd milk-sampling is operated, is excluded from the above table.—*Report of the Reorganisation Commission for Milk*, 1933, p. 52.

Routine clinical inspection, at least once every year, is compulsory in Scotland. Several counties have increased the frequency to (2 or 3 times a year on the recommendation of the Scottish Board of Health.—*ibid.*)

As to cows which are tuberculin-tested and are found to react, no record as to their ultimate use or disposal after eradication from the herd is kept. Tubercle bacilli can survive and retain their virulence in soil for as long as months and on grass for more than 60 days.—E. C. Maddock, *Brit. med. J.*, i/1932, 315.

The Milk Reorganisation Commission recommend a more effective and uniform administration of the Milk and Dairies Order and the Tuberculosis Order and the providing of a whole-time veterinary service, and that the three grades of milk be replaced by a single grade called "Special," of the standard of the present "Grade A" (tuberculin-tested) milk. They stress the compulsory routine inspection of all dairy cattle and would stimulate production of clean milk by paying a premium to producers of "Special Grade Milk" and the institution of a roll of "accredited producers."—*Report of the Reorganisation Commission for Milk (H.M.S.O.)*, *Brit. med. J.*, i/1933, 521.

Clean Milk

Milk falling below Grade A standard is an article so damaged that it cannot be regarded as satisfactory. If the producer disregards the necessary requirements (as to clean milk), he saves about $\frac{1}{2}$ d. per gallon, and saves a further 2d. per gallon by omitting to ensure that his herd is healthy. **Not for many years to come will the bulk of the milk supply be produced from tubercle-free herds**, but the production of milk of decent cleanliness is practicable. If the producers of the country want to do it, and the public demands it, the entire milk supply can soon be raised to Grade A, and all milk should be of that standard, whether consumed raw or pasteurised.—W. Buckley (National Clean Milk Society), *Brit. med. J.*, ii/25, 249.

Although many Orders have been passed safeguarding the health of cows in cowsheds, the only Order which would be of any real service would be one to **abolish cowsheds altogether**. It is only through open-air life and healthier conditions that tuberculosis is disappearing in human beings and this applies to cows, whose proper environment is the open field. The cowshed is the breeding-place of organisms. During the years 1920-24, of **16,249 cows slaughtered in Edinburgh, 7277, or 44·8%, were tuberculous**.—W. G. A. Robertson, *Practitioner*, 1927, 365.

There is hardly one of the 230,000 herds in the country which does not contain an infected animal. Steady progress is being made in the production of tubercle-free milk—in 1926 there were 252 herds, comprising 9,100 dairy cows, supplying pure milk. The greatest disadvantage to the farmer is the absence of a market for this milk. It can be retailed at prices only a little higher than the ordinary and it is certain that a public demand would lower these prices still further.—Leader, *Lancet*, ii/1927, 716.

It cannot be emphasised too strongly that it is *method* and not equipment which is the all-important factor in the production of clean milk. Owing to practical pioneer work done by the National Institute for Research in Dairying (University of Reading) about one-sixth of the milk supply of Reading is "Grade A" (T.T.): the retail price in the summer is $3\frac{1}{2}$ d. per pint and in the winter 4d., as compared with 3d. and $3\frac{1}{2}$ d. for ordinary milk. What has been done in Berkshire can be done in other counties. In the U.S.A., by means of what is known as the "**accredited herd**" and "**area eradication**" plans, there are **13 million cattle free from tuberculosis** and the districts where they are kept are so hemmed in with regulations and veterinary supervision that it is practically impossible to reintroduce among them infected cattle. The Tuberculosis Order throws the onus of diagnosis and reporting suspected cases on the owner, but the owner has not sufficient knowledge to make the diagnosis until the animal is in an advanced stage of disease: the deadly work has been done before the Veterinary Inspector sees the herd. The obvious remedy is periodical inspection of all cattle, and any owner found to have an animal in an advanced stage of tuberculosis which he should have reported should be fined and no compensation paid for slaughter. Only neglectful and indifferent owners would thus be penalised, and it would prevent the present scandal of cows being milked to the bitter end and, when no longer of use as milkers, reported and compensation claimed. **The inspection of the animal is obviously the job of the veterinarian, and it is an anomaly that this work is still too often left to the M.O.H. or the Sanitary Inspector**.—Prof. F. T. G. Hobday, *Lancet*, ii/1927, 738.

The nomenclature of the grades is very misleading. There is no doubt that *Grade A*, which is only *the third of the qualities* is considered by many people to be the *first quality*, while the Tuberculin-tested milk has not its proper position in the public mind because of the confusion of Grade A milk with that of the highest quality. There should be a revision of the nomenclature. Licensed graded milk still amounts to little more than 1% of the total milk used in Scotland. The liability of ineffective pasteurisation causes this to be a danger rather than a help by misleading people as to its safety.—Drummond Shiels (Parl. Notes), *Lancet*, ii/1928, 306.

The number of *cows which do not react to the tuberculin test* under the clean milk scheme has increased during the past five years by an average of about 1500 annually, and at the present time these number approximately 12,000. The tuberculin test in the end effects the elimination of all reacting animals from licensed herds. Sir George Newman said: "The only way of securing a satisfactory national milk supply is by setting up a high standard and asking producers to raise the standard of their milk accordingly."—*Daily Telegraph*, April 17, 1929.

What shall we do with the not clinically affected "reactor?" To let it drift to another herd is no solution: to destroy without compensation would ruin the farmer, and to pay compensation makes the cost too great. An alternative suggestion is to keep the "reactors" together upon separate farms containing nothing but "reactors." The cows would be paid for at a "two-thirds" value. Periodical veterinary inspection would weed out any becoming clinical cases and the cows would have to be kept under good open-air conditions. The milk would be pasteurised, and bacteriological tests would soon demonstrate the validity of the scheme. The calves from these cows would be segregated and fed on heated milk, and would grow up non-reactors and would serve as a storehouse of non-reacting cows for the herds depleted by the removal of "reactors."—W. G. Savage, *Brit. med. J.*, ii/1933, 909.

An adequate economic stimulus for building up tuberculosis-free herds must depend on a demand for milk from this type of herd. But where is this demand to come from? It is known that raw milk from tuberculin-tested herds is not free from the risk of carrying other diseases and it is difficult to imagine how any medical adviser is going to recommend, where a choice is available, the consumption of *raw, potentially dangerous certified milk* at a higher price, in preference to pasteurised safe milk of Grade A standard at a lower price.—*Brit. med. J.*, i/1934, 1035.

Approximately 17,500 cows were included in licensed herds on December 31st, and of 714 samples of certified and Grade A (T.T.) milks examined in Scotland in an investigation by the Medical Research Council only one yielded a positive result to the biological test.—*Rep. med. Offr Minist. Hlth, Lond.*, 1933, 169.

Report of the Economic Advisory Council Committee on Cattle Diseases (Cmd. 4591). The Committee, under the chairmanship of Sir Frederick Gowland Hopkins, was appointed on November 2nd, 1932, to consider practical measures for reduction of disease among milch cattle, to report on any changes desirable in present administrative practice, and, in particular, on the value and practicability of methods for reducing bovine tuberculosis and improving the milk supply. The Committee recommended: (1) *veterinary inspection should be made obligatory* on all local authorities and a veterinary service built up consisting largely of whole-time veterinary officers with training in veterinary State medicine; (2) *a list of tuberculosis-free herds (accepted herds) to be instituted*, and a list of herds whose owners are making efforts to free them of tuberculosis (supervised herds). Free veterinary advice and tuberculin-testing to be provided, with financial help where necessary, and a higher price to be paid for milk from tuberculosis-free herds by means of a levy on other types of milk. (*It is realised that the Tuberculosis Order, 1925, has done nothing to reduce the incidence of tuberculosis in cattle*); (3) All liquid milk sold for human consumption should be sold under official designation and whether consumed in the raw or pasteurised state must attain a certain standard of cleanliness on the farm. Four grades of milk are suggested: (a) *Certified milk*, from tuberculosis-free herds, to be sold raw, with no necessity for bottling on the farm; (b) *Pasteurised milk*; (c) *Sterilised milk*, i.e. milk raised to boiling-point or higher in a licensed plant; (d) *Milk (uncertified)*, which has not been heated, is not from tuberculosis-free herds, but which attains a certain hygienic standard.

Any authority with a population of over 100,000, and the L.C.C., to have the right to prohibit the sale of milk (uncertified) within 5 years of initiation of the scheme, providing it gives not less than 2 years' notice.—*Brit. med. J.*, i/1934, 1035.

A Memorandum on the Government's Milk Policy, presented to the Ministers of Health and Agriculture on March 27th, 1934. The carrying out of measures for the production of clean milk is largely provided for in the Milk and Dairies Order, 1926, and enforcement of this Order would result in considerable improvement in cleanliness. Dirty milk cannot be made clean by pasteurisation. Permissive powers of compulsory pasteurisation should be given to towns of 10,000 inhabitants and over, and adequate supervision of pasteurising plants by the local authority should be made obligatory. All raw milk that cannot be adequately pasteurised should be boiled. ***A pre-pasteurisation standard of cleanliness should be established.*** Permissive powers of pasteurisation of milk from tuberculin-tested herds would enormously stimulate the establishment of such herds. Pasteurised tuberculin-tested milk would be the cleanest and safest on the market. While in agreement with the Government on the desirability of cleaning up the milking herds, nothing short of the establishment of tuberculin-tested herds, on lines similar to those so successful in America, is worth serious contemplation. The £750,000 promised for improving purity of milk supply (*see Milk Act, 1934*), and the £500,000 for propaganda, should be devoted to furthering these suggestions rather than to the proposals at present contemplated by the Government.—Signatories to the Memorandum: J. A. Arkwright, J. C. Drummond, J. C. G. Ledingham, F. C. Minett, H. Raistrick, G. S. Wilson, and N. C. Wright.—*Lancet*, i/1934, 757.

MILK MARKETING SCHEME (APPROVAL) ORDER, 1933, made under Section 1 (8) of the *Agricultural Marketing Act, 1931*. Came into operation July 29th, 1933. (*A résumé.*)

Part II. The Board and the Regional Committees

Sections 5 to 37. The Board to administer the scheme to be called the "**Milk Marketing Board**," a body corporate, to consist after 30th June, 1934, of 12 regional members elected by the registered producers in the respective regions, three special members elected by the producers in general meeting, and two persons co-opted by the elected members. **Regional Committees** consisting of a member or members of the Board, together with one or more representatives from each of the counties in the region, to report to the Board on the operation of the Scheme in their respective regions.

Part III. Register of Producers

Sections 38 to 41. The Board to keep a register of producers, every producer being entitled to register therein, producers exempt from registration being those with not more than four milch cows (unless they sell milk by retail), and producers not carrying on the business of selling milk.

Part IV. Polls

Sections 42 to 47. On the coming into force of the scheme a poll of the registered producers to be taken on the question as to whether the scheme is to remain in force. (*Result of Poll declared in August 1935 showed a majority in favour of continuance of the scheme.*)

Part V. Financial Provisions

Sections 48 to 51. A fund to be established, and every registered producer to contribute not more than one shilling for every milch cow in his possession.

Part VI. Principal Powers of the Board

Sections 52 to 74. (54) *Producers neither registered nor exempt to be prohibited from selling milk.* (55) The Board may regulate sales of milk, i.e., the description of milk which may be sold, and the price at which it may be sold. (56) The Board may buy milk, produce commodities from milk (specified in Second Schedule), sell, grade, advertise and transport milk or milk commodities, encourage, promote or conduct agricultural co-operation among milk producers, or research and education in connection with production and marketing. (57) Shall draw up prescribed contracts for the sale of milk by registered producers, the purchase price being paid by the purchaser to the Board. (61) In the event of the registered producer being unable to find a customer under the prescribed terms of contract, it is the duty of the Board to accept the unsold milk. (62) *No registered producer may sell milk by retail without a "retail licence" issued by the Board.* (63) The Board shall prepare a *register of Accredited Producers* who will be entitled to an additional prescribed payment out of the fund ("Guaranteed Quality Premium") per gallon of milk sold.

MILK ACT, 1934. *Came into operation August 15th, 1934. (A résumé.)*

An Act to provide for temporarily securing to producers of milk, by means of payments out of moneys provided by Parliament, a minimum return in respect of milk used in the manufacture of milk products; for conditionally requiring repayment to the Exchequer of the amount of such payments; for making, out of moneys so provided, payments for the purposes of improving the quality of the milk supply and increasing the demand for milk; for regulating the manner in which milk is described for the purposes of advertisement and sale; for imposing and conferring certain duties and powers on boards administering milk marketing schemes; and for purposes connected with the matters aforesaid.

Section 9. Provides for the expenditure of not more than £750,000 during a period of four consecutive years, for the purpose of securing as far as practicable that the milk supplied for human consumption in Great Britain shall be pure and free from infection of any disease: it also provides that at the end of that period the Minister may make an order approving the payment by the Board to registered producers of a sum of not more than one penny per gallon in respect of any quantity of milk produced after the end of the period which complies with the requirements of the Scheme.

Section 11. Provides for the contribution of up to £1,000,000 in two years towards expenses incurred by Milk Marketing Boards in increasing the demand for milk.

Speaking in the House on May 31st, Dr. Walter Elliott said that, although the Hopkins Committee (see p. 410) reported that the total eradication of bovine tuberculosis from all herds was the only complete solution of the problem of tuberculous milk, it was impossible at present for the Milk Board to bear the cost of the scheme for establishing tubercle-free herds as well as the scheme for the Roll of Accredited Producers.—*Brit. med. J.*, i/1934, 1057.

Roll of Accredited Producers

The establishment of a Roll of Accredited Producers has been advocated for some time by the Milk Marketing Board (Thames House, Millbank).

The following is a brief outline of the Scheme as it appears in a brochure published by the Board (August, 1934).

"Accredited Milk," it is stated, will be "milk from cows that have been clinically tested; from farms where scrupulously clean methods are practised—and itself a product subject to bacteriological tests."

Producers will be encouraged to conform to the new standard by the payment of a bonus (a premium of 1d. per gallon over the "pool" price) for every gallon of accredited milk produced, out of a central fund raised by means of a small levy on all milk produced.

The Board seeks the co-operation and support of County and Borough Councils, who are asked to undertake the necessary inspection, veterinary and bacteriological duties.

Details of the scheme include registration preceded by a clinical examination of all cattle in the herd, and removal of any considered by the examining veterinary surgeon to be a danger to the milk supply; inspection of premises and methods of production followed by supervisory visits; and compliance with the requirements regarding bacteriological examination, and with the following standards: ***Bacterial count not exceeding 200,000 per ml.; B. coli absent from 1/100 ml.***

The fulfilment of all the above requirements to be certified by the responsible official in each case.

After registration, it is required that ***animals must be inspected at intervals of not more than 6 months;*** the methods of production must continue to comply with the standard of efficiency, and the bacteriological standard must conform to requirements, ***a minimum of 3 samples to be taken annually,*** each within a definite period of 4 months, e.g. January to April, etc.

Penalties are provided for failure to comply with the conditions.

It was hoped that the Roll would be introduced on these lines at the beginning of 1935. This was not found possible, but the following account from *The Times* (21/2/1935) indicates that the Accredited Roll will be established on May 1st, the basis of agreement being the present Grade A Scheme of the Ministry of Health.

"The County Councils Association and the Milk Marketing Board have reached a basis of agreement for the establishment of a roll of accredited milk producers on May 1. The Association of Municipal Corporations will recommend approval of this agreement to their executive council.

The three bodies have been conferring for several months on the most practical means of ensuring a more general standard of purity in milk, and agreement on the main points of a scheme was reached on February 19th. It was then decided that on and after May 1 a registered producer who presents a Grade "A" certificate to the board will be entitled to have his name placed on the accredited roll and to receive from the board a premium on all graded milk supplies, irrespective of the use to which they might be put by the buyer.

It is anticipated that the premiums or bonuses will amount to 1d. a gallon. The sums thus distributed by the board to accredited producers will be drawn from a central fund to be created by means of a fractional levy on every registered milk producer. Producer-retailers will be entitled to qualify for these bonuses. Dairy farmers who are now licensed for the production of Grade "A" milk will qualify automatically and others who intend to earn the new bonuses must take the necessary steps to have their farms licensed by the appropriate local authority.

To obtain a licence a producer must apply to the authority in his area for his herd to be clinically examined and his milk to be sampled.

The initial sampling and veterinary inspection must take place at least one month before the producer's name is placed on the board's roll. It is believed that in some areas inspection and sampling are undertaken on farms licensed for Grade "A" production without any charge being made to the producer, and it is a recommendation of the County Councils Association that this practice shall continue in such cases. In counties where these services have not been provided *gratis* it is to be recommended that the charge to producers shall be as low as possible.

In every case the accredited producer will pay to his local authority the annual licence fee of £1 1s., and the cost of the pre-licence clinical test and sampling will also be borne by the producer in districts where the authorities make a charge. **The subsequent herd inspections (four a year)** will, it is confidently hoped, be free in some areas, and at only a small cost in others.

Potential accredited producers will be concerned as to how far in its transit from the farm they are to be held legally responsible for maintaining the standard of their milk, as laid down in the Milk (Special Designations) Order, 1923. The whole scheme relates to the production of milk, and tests which will put the onus on the farmer can be made only while the milk nominally is in his possession—i.e., not later than the time of its delivery in sealed containers to the buyer's depot or dairy. The wholesale producer's responsibility ends at that point.

The Grade "A" (T.T.) and certified producers who sell their milk through the board will be entitled to be entered on the roll of accredited producers and earn the premium."

The Tuberculosis (Attested Herds) Scheme (England and Wales). *Came into operation on February 1st, 1935, under the Milk Act, 1934.*

While the Milk Board proposals for an Accredited Scheme aim at raising the general standard of cleanliness and purity of the milk supply, the Attested Scheme of the Ministry of Agriculture is ***directed more specifically to the eradication of tuberculosis from dairy herds.*** The scheme offers a special inducement to this end to dairy farmers. It carries the improvement of the milk supply a stage further than the Milk Board's Accredited Scheme, and those who qualify for the register of attested herds will earn an extra 1d. per gallon from Government funds in addition to the bonus to be offered under the Accredited Producers' Scheme.

The terms fixed for the Ministry of Agriculture's attested register appear to be more exacting than those of the Ministry of Health's Grade A (T.T.) Milk, and it has been suggested by experienced producers that the provisions of the Ministry of Agriculture's scheme are so drastic as to make it unworkable in practice. They have found, in spite of all precautions, that ***it is well-nigh impossible to keep a dairy herd absolutely free from reactors over a period of years,*** and that almost always one or two cows fail at the six-monthly tuberculin tests.

Under the present scheme an owner may make application to the Ministry for an official test, provided that no reactors were found in the herd on the occasion of the last two private tests, if carried out with due regard to the intervals prescribed. The application should be supported with certificates to this effect signed by the veterinary surgeon who carried out the tests on behalf of the owner. A certificate of attestation is valid for one

year. It will be renewed annually, if desired by the owner of the herd, after a further official test of all cattle in the herd, provided that no reactors are disclosed and the Ministry is satisfied that the herd and premises continue to be suitable for attestation.

If any reactor is found, the renewal of the certificate of attestation will be suspended, *the reactor immediately isolated and disposed of* as quickly as possible, and the premises thereafter disinfected. A further official test of the non-reactors is to take place not earlier than 60 days after completion of the disinfection. If this reveals no reactor the certificate of attestation will be renewed for 6 months. If any reactor is found as the result of the re-test it must be removed as before and the premises again disinfected. A second official test will then be carried out after the expiration of 60 days, and if any additional reactor is found the herd will be removed from the register of attested herds and the certificate of attestation will be cancelled.

These *official tests will be carried out without charge to the owner*, and while his herd is on the register the Ministry of Agriculture will pay him a bonus of 1d. per gallon, on all milk sold, from the fund provided by the Milk Act 1934.

The fundamental principles of successful eradication are stated to be (Advisory Leaflet, No. 223):—

- (i) the tuberculin testing of the whole herd,
- (ii) the separation of reactors from non-reactors, and
- (iii) the thorough disinfection of the premises to be occupied by the non-reactors.

The soundest and quickest method of eradication consists in adequate tuberculin testing and the prompt slaughter of all reactors, but as the percentage of reactors in the majority of the herds of this country is high, unfortunately this method is precluded on grounds of cost. The elimination of reactions by sale is less costly, but animals showing clinical signs of the disease or giving tuberculous milk must be reported and dealt with under the Tuberculosis Order of 1925. In addition to the risks of re-infection of a herd by contact with infected stock, contaminated premises, pastures, or water, there is also the danger of introducing the disease by pigs or poultry. Pigs constitute a very likely source of infection as about 50% of tuberculous infection in these animals is of the bovine type. Manure from reactors is also a potential source of infection. That other means of alleviation of the situation are not being neglected is shown in the statement in Parliament (March 1935) by the Minister of Agriculture that a final report is expected shortly on the tests of Dr. Spahlinger's bovine vaccine treatment for animal tuberculosis which have been carried out by the Northern Ireland Ministry of Agriculture.

Advantages of Eradicating Tuberculosis in Cattle.

In a leaflet issued by the Ministry of Agriculture, with the above title, it is pointed out that, under the Tuberculosis Order 1925, 350,550 animals were examined and 20,908 slaughtered in 1933, the total amount of compensation paid being £71,827.

During the years 1926-33 (inclusive) £511,221 was paid as compensation for animals suffering from tuberculosis. The total market value of all the cattle slaughtered was £1,265,105, and the value of those animals had they been healthy would have been very much greater. If to this amount is added the depreciation in the value of cattle affected with forms of tuberculosis not dealt with in the Order it will be seen that the total loss sustained reaches an enormous sum.

This progressive wasting disease leads to reduced milk yield, shorter milking life, increased susceptibility to other diseases and loss in beef-value. In addition, milk from affected cows may contain tubercle bacilli and thus constitute a source of infection to persons, particularly children, consuming it.

Diseased cows cannot long withstand the strain of high milk production. *In addition the average milk yield per cow has been shown to increase as tuberculosis eradication progresses.*

CONSUMPTION OF MILK

The National Milk Publicity Council is constituted of representatives of the Ministry of Agriculture, Ministry of Health, Board of Education, Society of Medical Officers of Health, the Milk Marketing Board, producers and distributors, and the Co-operative Movement. It has area organisers in the eleven areas covered by the Milk Marketing Board to organise the campaign for educating the people on the food value of milk, by lectures, demonstrations, films, exhibitions, etc. Under *the N.M.P.C. Scheme for milk in schools*, when the children had $\frac{1}{3}$ pint of milk for 1d., one million children came under the scheme, consuming 10,000,000 gallons of milk. Since October, 1934, under the revised scheme, when, through the help of the Government, the cost of this ration was reduced to $\frac{1}{2}$ d., the number of children increased to 2,750,000. It is the idea of the Council that ultimately every child will have its milk ration at school. As there are over $5\frac{1}{2}$ million children in attendance at our elementary schools, much educational work lies in front of the regional workers of the Council in co-operation with the educational authorities.

Rapidly increasing amounts of milk are now being consumed in mines and factories.

The figure for rail-borne milk alone in 1928 was 131 million gallons, as compared with 72 million gallons in 1923 and 117 million gallons in 1927, but owing to the increasing use of road transport reliable figures for the total annual consumption in more recent years are not available.

Milk Consumption and the Growth of School-children.

Investigations carried out in an institution near London containing 600 boys showed that an immediate improvement in physique followed the use of fresh cows' milk, recently pasteurised, as an additional item of food, and this improvement was maintained over a period of from one to three years.—H. C. Corry Mann, *Spec. Rep. Ser. med. Res. Coun., Lond., No. 105, H.M.S.O., 1926; Brit. med. J., ii/1926, 318.*

The addition of milk (whether "separated" or "whole") to the diet of school-children gave an increase of 20% in height and weight, and improvement in the general condition. *Separated milk* of great value for promoting growth—its nutritive value for children has been under-estimated.—J. B. Orr, *Prelim. Rep. on Tests to the Scottish Bd. of Health, Lancet, i/1928, 203.*

Dr. Orr's conclusions were more than justified. The great value of additional milk is clearly demonstrated for school-children of all ages, the increase in height in milk-fed groups being actually 1.21%, and in weight 3.75% greater than in the first test, the initial improvement being continued over the second year. The value of separated milk is again shown, there being no significant difference in height and weight (except in the 6-year old group) between the separated milk and the whole milk groups.—G. Leighton and Mabel L. Clark, *Second Prelim. Rept. on Tests to the Scottish Bd. of Health, Lancet, i/1929, 43.*

It would be a mistake to conclude from these investigations that separated milk is as good as whole—the home diet was an unknown factor in the experiments. Height and weight are not the only criteria of good health—another important manifestation is the power to resist disease, and subsequent reports would be more valuable if clinical histories were given. At the same time, the fact that the addition of one pint of milk daily produced such striking improvement confirms the contention that large classes of the population suffer as a result of taking too little. Unfortunately, the use of whole milk and butter is expensive, but these results justify their replacement by separated milk and

margarine containing vitamin A. A diet of porridge, brown bread, separated milk and vitamin A margarine would cover almost all nutritive requirements at a minimum of cost. The distribution of such a diet (at any rate to children, and nursing and expectant mothers) in the distressed areas would prevent under-nutrition and would be not only a measure of properly-regulated charity but one of wise economy.—*Lancet*, i/1929, 29.

See also *Milk Consumption and the Growth of School Children*.—Leighton and McKinlay, H.M.S.O., 1930.

PASTEURISATION

From the public health point of view the term "Pasteurisation" should be confined to the process of heating milk to ***not less than 145°F. and not more than 150°F. for 30 minutes***, and experience shows that when properly carried out this is sufficient to destroy virtually any pathogenic organisms without producing appreciable change in the physical and chemical characters of the milk. *B. tuberculosis*, *B. diphtheriæ*, *B. dysentericus*, *B. typhosus* and other organisms of the *typhoid-paratyphoid* group, together with the virus of foot-and-mouth disease, are all destroyed by pasteurisation. Under certain conditions a small proportion of tubercle bacilli may escape actual destruction, but their virulence is so impaired as to make them harmless. Some strains of streptococci may survive, but not those believed to be responsible for septic sore throats. Pasteurisation therefore affords a simple means of rendering milk reasonably safe as regards risk of transmitting disease. Pasteurisation does not destroy all the non-pathogenic organisms, though their number may be reduced by 99%. The sporing organisms and a small proportion of lactic acid bacteria survive. The great reduction in lactic acid bacteria, enabling milk to keep fresh longer, is the chief advantage which pasteurisation offers from the commercial point of view. Generally speaking, the number of bacteria in milk after pasteurisation is greater in milk which contained a large number of bacteria before pasteurisation than in milk which originally contained relatively few bacteria—this is of practical importance, ***the bacterial content of pasteurised milk gives an indication of the bacterial content before pasteurisation***.

There is no appreciable change in the physical and chemical characteristics of properly pasteurised milk. When milk is pasteurised at 145°F. for 30 minutes the "cream line" is hardly affected, but at 148°F. it may be decreased by 40%—the integrity of the "cream line" is important commercially. ***Pasteurisation causes no appreciable change in the milk proteins***, but at 150°F. about 5% of the milk albumin is rendered insoluble. Pasteurisation does not cause the soluble calcium and magnesium phosphates to separate out, and has only a slight effect on the enzymes. Vitamins A and B are unaffected, but vitamin C is destroyed.

The ideal milk supply would of course be milk obtained from perfectly healthy cows under the cleanest conditions, consumed immediately with the least possible manipulation, but in a highly

urbanised country such as England this is impossible, and without some process for preserving the keeping quality of milk a proportion of the population would be forced to curtail or even do without a very important food. By subjecting the average milk of this country to pasteurisation, the destruction of any pathogenic organisms is virtually assured and its keeping qualities are improved.

Experimental evidence does not bear out the assertion that bacteria grow faster in pasteurised than in raw milk—the rate of bacterial increase is approximately the same. It is alleged that pasteurisation will encourage lack of cleanliness in milk production, but this is not so, as milk so stale as to be unfit for sale will not have its flavour improved by pasteurisation—moreover, only a milk sufficiently clean before pasteurisation would comply with the requirements of a bacterial count after pasteurisation.

The *nutritive qualities of milk do not appear to suffer appreciable change from pasteurisation, except in respect of anti-scorbutic property*, which can be corrected by orange juice. It is held by some that changes referred to in the physical and chemical characters are indicative of possible subtle alterations in nutritive value, not easily detected or estimated, which are perhaps of far-reaching importance. Even assuming, however, some depreciation of these hypothetical nutritive values, it is not unreasonable to assume that the impairment would be of the same order as in those characteristics capable of observation, i.e., partial and slight impairment rather than complete destruction, and *from a practical standpoint the positive advantages of pasteurisation outweigh any possible slight depreciation of nutritive elements*, the existence of which is hypothetical. Extensive experience of feeding children on pasteurised milk shows it to be as well borne by them as raw milk and (except in anti-scorbutic property) equally nutritious.—Notes on the Pasteurisation of Milk, by J. M. Hamill, *Rep. publ. Hlth med. Subj., Lond.*, No. 17, 1923.

The changes undergone by milk as a result of pasteurisation by the holder's process may be summarised as follows: ability of fat globules to separate out is impaired, *causing slight diminution in the cream line*: about 5% of the albumin is coagulated: there is an alteration in the equilibrium between the calcium and phosphate ions, a diminution of about 5% occurring in the soluble fractions; the sensitivity of calcium caseinate to rennin coagulation is affected, the coagulation time being shorter, and the rennin coagulum is of a looser texture than in raw milk; vitamin C is destroyed to the extent of about 50%; the pathogenic organisms that may be present, together with a variable proportion of non-pathogenic bacteria, are killed. The *effect on enzymes, bactericidal property, antibodies and lactic acid bacteria dismissed as irrelevant*. No diminution in nutritive value occurs as a result of pasteurisation that cannot easily be remedied by the simple addition of orange or lemon juice and cod-liver oil.—J. D. Stirling and J. H. Blackwood, *Hannah Dairy Res. Instit., Glasgow, Brit. med. J.*, i/1933, 792.

The process may be approximately carried out by plugging convenient sized bottles filled with the quantity for one meal, heating in a pan surrounded with water to nearly boiling-point, removing from the fire, covering with a clean cloth and allowing to stand for half-an-hour. Then cool rapidly, and store in a cool place.

Thermal Death-point of the Tubercle Bacillus in Milk.

As a result of experiments the following conclusions have been drawn:

(1) By using 25 strains of tubercle bacillus no wide difference in the death-point was found.

(2) The thermal death-point is practically similar for human and bovine types.

(3) Previous variations in results due to too little care in carrying out experiments.

(4) 20 minutes exposure at 60°C. required to prevent milk so treated carrying infection to the guinea-pig.

(5) 5 minutes at 70°C. required to ensure the same result.

(6) Of the two combinations of time and temperature factors the former excels the latter when the *food value* of the treated milk is also considered.

(7) Until bovine tuberculosis can be stamped out at its source pasteurisation is the only safe method of rendering milk safe for human consumption.—F. W. Campbell Brown, *Lancet*, ii/1923, 321.

The raising to 190°F. makes milk perfectly safe from contamination with *B. tuberculosis*, and this does not impair its nutritive value.—N. Raw, *Brit. med. J.*, i/1921, 596.

Pasteurisation at 145°F. for 30 minutes ensures a non-infective milk so far as T.B. is concerned.—R. G. White, *Lancet*, i/1926, 222. Pasteurisation in *closed vessels* at that temperature for 30 minutes, then cooling to under 40°F. renders the milk free from tubercle bacilli and all other pathogenic bacteria.—S. G. Moore, *Brit. med. J.*, ii/1926, 855.

The number of bacteria reduced by pasteurisation is often only slight as compared with raw milk and a tremendous increase may take place during the cooling process.—Prof. J. M. Beattie, *Proc. Nat. Milk Conf. on Pasteurisation, Lond.*, 1923—quoted by C. Dukes, *Bacteriology of Food*, 1925.

The **organisms found in milk** may be classed as follows:—(i) Acid producing (100 varieties), the principal member of which is *B. acidi lactici*; (ii) *B. acidi butyrici* (has very resistant spores, not killed by pasteurisation); (iii) those responsible for fermentation to alcohol, as koumiss, butter milk, red milk, blue milk, etc.; (iv) the mould *Oidium albicans* produces thrush in infants' mouths; (v) *B. tuberculosis* (vi) *Streptococci* associated with contagious mammitis; (vii) *B. diphtheriæ*; (viii) *B. coli communis* and *B. typhosus*.

Milk-borne infections. Discussion by the Section of Bacteriology, B.M.A. Cent. Meeting, 1932. (*Brit. med. J.*, ii/1932, 314).

Milking machines satisfactory when in good condition, but a mechanical defect or faulty cleaning might result in a very heavy pollution of milk.—Otto Moltke. Streptococcal mastitis very common in milch cows; 20% of the mastitis in cows might be due to streptococci of human origin.—F. C. Minett. Contagious abortion very common among cattle in this country and probably half our herds contained infected cows. Pasteurisation the only safeguard.—Sir W. Dalrymple-Champneys. Of retailed raw milk samples about one-sixth contained tubercle bacilli and over one-third *Brucella abortus*.—C. P. Beattie.

Properly controlled pasteurisation of milk affords a definite safeguard against milk-borne infection, but the eradication of bovine tuberculosis and contagious abortion is infinitely preferable.—S. R. Douglas, *Brit. med. J.*, ii/1932, 198.

Epidemic sore throat at Brighton—traced to milk. Seven fatal cases.—*Brit. med. J.*, i/1930, 128.

No milk-borne epidemic traced to pasteurised milk or cream. The septic sore throats at Brighton were due to raw milk.—P. B. Tustin, *Brit. med. J.*, ii/1930, 586.

A milk-borne epidemic of septic sore throat in Portland, Oregon. 487 cases and 22 deaths caused by drinking raw milk from one dairy. Similar strains of hæmolytic streptococcus of human type obtained in almost pure culture from the inflamed udder of a cow, from one milker's throat and from the throats of numerous sore throat patients and contacts.—R. L. Benson and H. J. Sears, *J. Amer. med. Ass.*, per *J. trop. Med. (Hyg.)*, 1923, 257.

Outbreak of milk poisoning in Aberdeen affecting 300 persons—acute diarrhœa and vomiting, but no deaths—traced to milk containing organisms of typhoid-dysentery group, apparently derived from a byre or farm worker.—*Brit. med. J.*, ii/1925, 229.

While 26 samples of certified milk were free from tubercle bacilli, 17 of the samples contained *Br. abortus* and 16 mastitis streptococci. Of 39 Grade A (T.T.) samples 1 contained tubercle bacilli, 31 *Br. abortus* and 29 mastitis streptococci. Of 43 samples taken from raw milk coming to London in 3000-gallon tanks **every one contained virulent tubercle bacilli** and 27 *Br. abortus*. After pasteurisation not a single one contained either of these organisms in the living state.—F. C. Minett and E. J. Pullinger, *Brit. med. J.*, ii/1933, 1080.

5483 samples of milk coming into and distributed in Aberdeen, Dundee, Edinburgh and Glasgow were examined for tuberculous infection by the Hannah Dairy Research Institute (*Spec. Rep. ser. med. Res. Coun., Lond., No. 189*). Composite churn samples of raw milk from individual farms were infected to the extent of 10%; raw tank-milk samples 37·5%; flash-pasteurised milk 8·2%; holder-pasteurised milk 2·8%; and retailed milk rather over 5%. Of 714 samples of certified and Grade A (T.T.) raw milk only one sample was infected. All the positive samples from holder-pasteurised milk were taken from three types of plants, the remaining five types yielding perfectly satisfactory milk; faulty pasteurisation probably due to improper design of plant or inefficient operative procedures.—*Brit. med. J.*, ii/1933, 1225.

Of 101 samples of milk from 45 tuberculin-tested herds, 1 contained tubercle bacilli and 70 *Br. abortus*. Samples from 63 3000-gallon rail tanks showed all to be contaminated with tubercle bacilli and 53 with *Br. abortus*. Neither organism survived pasteurisation in corresponding samples. **Samples of tank milk had to be diluted from 10 to 1000 times before tuberculous infectivity for guinea-pigs was lost.** Samples of udder milk from cows with tuberculous mastitis could be diluted one million times with clean milk without infectivity for guinea-pigs being destroyed.—E. J. Pullinger, *Lancet*, i/1934, 970.

Copper in Milk. Minute amounts of copper added to milk appreciably reduce the anti-scorbutic vitamin in the course of heating. Where the pasteurising plant is not in good repair or is not well cared for, there exists real danger of copper contamination, which may accelerate the destruction of accessory food factors.—*Brit. med. J.*, i/1924, 874; see also *Brit. chem. Abstr. (A)*, 1928, 1152.

Raw Milk v. Pasteurised

That there is a danger of wide-spread pasteurisation affecting the health of children cannot be denied. The diminished vitamin supply can be made good, but the means or the opportunity to supplement the diet in this way are not always available. The alteration in the relationship of the **diffusible** and **non-diffusible lime salts** on heating milk is also important from the bone-formation view. 26·4% of the total calcium in fresh milk is diffusible and in pasteurised milk it is 20·4%. Experiments in New York as to the relative efficiency of certified and pasteurised milk showed that the former alone gave greater increase in body weight in babies than the latter, whether alone or with orange-juice and cod-liver oil—the increase with certified milk was 14%, with pasteurised milk alone 1·7%, plus orange-juice 7·9%, and plus orange-juice and cod liver oil 9·5%. Other experiments showed that pasteurisation causes precipitation of the calcium, which adheres to the sides of the vessel—with rats fed on pasteurised milk the growth was half normal, while those fed on pasteurised milk plus washings from the vessels showed normal growth. The indiscriminate use of pasteurised milk by the great majority of the population is not to be recommended.—C. Maddock (Hon. Sec., Grade A (T.T.) Milk Producers Assn.), *Lancet*, i/1927, 54.

A comparison of a group of 1920 children who had received no milk whatever but heated milk, with a group of children fed on raw milk for more than half their lives showed the height and weight curves to be practically identical.—*Publ. Hlth Rep., Wash.*, 1932, No. 39, *Brit. med. J.*, ii/1932, 849.

There are no human experiments which demonstrate that pasteurised milk is less nutritive to the young child than raw milk, while there is a vast mass of clinical experience to show that **heated milk has been consumed for years by infants and young children without any detectable deterioration in the nutritive condition.**—W. G. Savage, *Lancet*, i/1933, 429, 485.

The Lanarkshire Milk Experiment.

Children of the same initial height and weight within fixed limits, showed that (1) extra milk (raw or pasteurised) generally increased the gain in height over controls to an equal extent, except that on pasteurised milk older girls gained more than younger girls; (2) extra milk increased gain in weight, more in girls than in boys, more in older girls than in younger and the difference associated with age was greater with raw milk than with pasteurised; (3) ***on the selected material there was no evidence of the superiority of either raw or pasteurised milk in increasing growth rate.***—E. M. Elderton *Ann. Eugen., Camb.*, 1933, 5, 326.

There is no significant difference in the gastric digestion of boiled and raw milk, and it may be concluded that ***digestion of milk is not adversely affected by boiling.***—J. W. Ogilvie and O. D. Peden, *Lancet*, ii/1934, 78.

The Milk Marketing Board is arranging for a careful investigation to be made of the merits of fresh milk and pasteurised milk for general consumption. While pasteurisation may have become a commercial necessity in dealing with large quantities of milk brought from a distance, there is a strong case for encouraging the distribution of reliable milk, such as milk from accredited herds, in the natural state.—Sir Arnold Wilson, M.P., at the annual general meeting of Milk-recording Societies (*The Times*, 25/3/1935).

Detection of Pasteurisation

To 5 ml. of the milk add 1 ml. of benzidine acetate solution 1% and a drop of acetic acid; after shaking, 3 ml. of H_2O_2 are run on to the surface of the mixture.

Unheated milk gives	Blue colour.
Heated milk, about 60°	Faint blue.
Heated milk, above 70°	No colour.

Arnold's Test gives similar reactions, an old tincture of guaiacum being used as reagent, and dropped on to the surface of the milk. Freshly prepared tincture requires the addition of hydrogen peroxide.

A Bacteriological Test to Detect Pasteurised Food. When food has been pasteurised at 60°, subsequent heating to any temperature less than this does not appreciably reduce the number of bacteria, but heating above 60° would considerably reduce the number. On the other hand, the bacteria in unpasteurised food are reduced progressively as temperature rises from 50° to 60°.—C. E. Dukes, *Brit. med. J.*, ii/1929, 907.

Phosphatase Test for Efficiency of Pasteurisation. It is well known that if the British Official Stipulations regarding pasteurisation are properly carried out any pathogenic organisms which are likely to be present in ordinary raw milk are destroyed, and that with a margin of safety. Hitherto no satisfactory method has been available for controlling the efficiency of the process by examination of the product. Such a test has, it is believed, been discovered, and it is described in some detail elsewhere (Graham and Kay, *J. Dairy Res.*, 1935, 6). (In the press). It depends on the finding that phosphatase, an enzyme whose presence and quantity can be detected and determined readily and which is present in all raw milk, has the extremely convenient property of being almost completely destroyed by "legal" pasteurisation, but not being completely destroyed if the milk is heated at a lower temperature than 145°F. or for a shorter period than thirty minutes (Graham and Kay, *ibid.*, 1933, 5, 54). Over all ranges of temperature and time *Myco-bacterium tuberculosis* is destroyed rather more quickly than the phosphatase, so that a heated milk which does not contain the enzyme has presumably been sufficiently heated to destroy any *M. tuberculosis* originally present and hence (North and Park, *Amer. J. Hyg.*, 1927, 7) all the common pathogenic organisms.

A table is given showing the results of the phosphatase test on designated pasteurised milk sold to the public or to children under the "milk in schools" scheme in London Boroughs and elsewhere. The authors consider that their recent application of the test permits the following statements:—

- (1) "A large number of pasteurising plants of all sizes both in London and elsewhere are either inherently functionally inefficient or unsatisfactorily operated.
- (2) "The properly designed and supervised plants, whether large or small, provide a satisfactory product. The phosphatase test has proved a valuable aid in this supervision.
- (3) "Of the large firms a majority, but by no means all, use efficient plants and/or methods,

(4) "The milk sold to school-children as 'pasteurised' appears, in a large proportion of the cases examined, to have been pasteurised in a particularly amateurish way.

(5) "In view of the large percentage of designated 'pasteurised' milks on the market which have been grossly underheated it is particularly desirable that all milk, and especially milk which is to be consumed by school-children, should reach a reasonable hygienic standard—say Grade A—before pasteurisation."—H. D. Kay and F. K. Neave, *Lancet*, i/1935, 1516.

Faulty pasteurisation. *There is reason to believe that much pasteurisation is pasteurisation in word only and not in fact.* In some cases pasteurising appliances are badly designed and in others carelessly and improperly operated, so that the milk is not really pasteurised and may contain living tubercle bacilli. Local authorities should satisfy themselves on these points before issuing licences. A useful indication of efficient working of a plant is given by the *B. coli* content of the finished milk, but ***samples must be taken on issue from the holder of the pasteurising plant.*** *B. coli* should be absent immediately after pasteurisation.—*Rep. med. Offr Minist. Hlth, Lond.*, 1933, 170.

The Supervision of Milk Pasteurising Plants, by Sir W. Dalrymple-Champneys, Bt.—*Rep. publ. Hlth med. Subj.*, No. 77, 1935.

BACTERIOLOGICAL TESTS FOR GRADED MILK

Memo. 139/Foods (Ministry of Health, 1929)

Standards

1. The following bacteriological standards for the various classes of graded milk are prescribed by the Milk (Special Designations) Order, 1923:—

<i>Certified Milk and Grade A Milk Pasteurised.</i>	The milk must not contain more than 30,000 organisms per ml., and must not contain coliform bacillus in 1/10 ml.
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<i>Grade A (Tuberculin Tested) Milk and Grade A Milk.</i>	The milk must not contain more than 200,000 organisms per ml., and must not contain coliform bacillus in 1/100 ml.
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<i>Pasteurised Milk.</i>	The milk must not contain more than 100,000 organisms per ml.
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Sampling

2. Where the milk to be sampled is contained in bottles each sample should consist of one bottle (with seal unbroken) taken anywhere between the place of bottling and the consumer. Where the milk to be sampled is not contained in bottles, samples should be taken and despatched in specially sterilised 4-oz. or 6-oz. bottles, each bottle being properly fastened and sealed.

3. On collection, the bottles must be transferred forthwith to a carrying-case and well packed in ice, and must be kept in this condition until plated at the laboratory. (This precaution may be dispensed with only if the bacteriologist considers it unnecessary on account of the proximity of the laboratory to the place in which the samples are collected.)

4. If the plates are not made within 30 hours of the time of milking or, in the case of pasteurised milk, of the time of pasteurisation, the additional time must be stated on the report, and in any case must not exceed 12 hours.

LABORATORY TECHNIQUE

5. In order that the results obtained by different bacteriologists engaged in the examination of official samples of graded milk may be comparable, the adoption of a strictly uniform technique is highly desirable. The technique described below has been found to be satisfactory, and should for this reason be universally adopted.

Medium for Plates

6. To prepare the medium take—

Tap water	1000 ml.
Peptone	5 g.
Lemco	3 g.

7. Dissolve by heat and filter hot through paper, add 15 g. agar (best quality, clean); dissolve by heat, titrate with phenolphthalein. The reaction will usually fall between +5 and +10 on Eyre's scale, and the medium may then be used without any further adjustment of titre. If a batch does not fall within these limits, it should be brought within them by adding the minimum amount of acid or alkali.

8. Cool to 45°, then bring to boiling-point and filter through paper or absorbent cotton until clear. Eggs must not be used for clearing.

9. Distribute in flasks and sterilise for 30 minutes at 15 lb. pressure, or for 20 minutes on three successive days in the Koch steriliser.

Dilutions

10. Dilutions of (a) 1:10, (b) 1:100 and (c) 1:1000 should be made in bottles containing accurately measured quantities of sterile water and fitted with glass stoppers; or by some other means which makes shaking possible. The dilution should be:—

(a) 90 ml. of water plus 10 ml. of milk;

(b) 90 ml. of water plus 10 ml. of the (a) dilution;

(c) 90 ml. of water plus 10 ml. of the (b) dilution.

11. At least two pipettes are required for each sample, one for dilution (a), and another for dilutions (b) and (c); the latter pipette should be washed out ten times in each dilution as it is made. Alternatively, a separate pipette may be used for each dilution. Straight-sided pipettes (not bulbed) should be used.

12. In making dilutions the original sample and each dilution bottle must be shaken 25 times, each shake being an up-and-down motion, with an excursion of about 1 foot.

In making the plate, put the required quantity of diluted milk into a sterile tube (5 in. by 1 in.) and add about 15 ml. of melted agar cooled to 45°; then pour the mixture into a Petri dish (3½ in. internal diameter). The depth of the agar in each Petri dish should be uniform.

13. Not more than half an hour should elapse between the dilution of the milk and the pouring of the plate.

14. After the agar has thoroughly hardened, incubate for 48 hours at 37°.

Counting of Colonies

15. If among the different dilutions there are plates containing from 30 to 300 colonies, these should all be counted, and the number, multiplied by the dilution, reported as the final count. If there are no plates within these limits, that which comes nearest to 300 should be counted. No plate that contains less than 20 colonies should be counted, unless there are no plates with a larger number. If the number of colonies on a plate is over 300, a part of the plate may be counted and the whole plate averaged.

"Coli" Tests

16. For Certified milk and Grade A milk Pasteurised: three tubes, each containing 10 ml. of bile-salt lactose peptone water,* and a Durham's fermentation tube, should be inoculated each with 1/10 ml. of the sample under examination, and incubated at 37°. For Grade A (Tuberculin Tested) and Grade A milk, three tubes should each be inoculated with 1/100 ml. of the milk.

* This should be prepared as follows:—5 grammes each of sodium taurocholate and lactose, 20 grammes of peptone, and 1 litre of water are heated together until the solids are dissolved. The mixture is filtered and sufficient strong neutral litmus solution is added to give a distinct colour. The medium is then distributed into fermentation tubes, and sterilised by steaming for 20 minutes on 3 successive days.

17. An uninoculated control tube should also be incubated.

18. The tubes should be examined for acid and gas production at the end of 48 hours. The milk is regarded as satisfactory in respect of this test if two out of the three tubes are found to be free from acid plus gas after 48 hours' incubation.

Reports

19. The results of both bacteriological examinations should be recorded on a form similar to that contained in the Appendix to this Memorandum, and the report should be sent to the Ministry or the Licensing Authority immediately on the completion of the examination.—Ministry of Health, Whitehall, S.W.1, February, 1929.

Until a more standard practice is adopted by bacteriologists (e.g., a faithful carrying out of the technique for examination of graded milks as set out in Memo. 39/Foods by the Ministry of Health) little value can be placed upon reports received, and both time and money are being wasted in submitting milk samples for examination. A quart bottle of pasteurised milk was shaken and divided into 6 parts in sterile bottles, two of which were submitted to each of three laboratories. One report gave a bacterial count of 9270 per ml. and another 3,400,000 per ml. for the same milk, and the results obtained from one laboratory were 147,000 and 3,400,000. To withdraw a licence upon such unreliable data would be most unjust. It is possible that the milk in some cases is insufficiently shaken before examination; more uniform results would be obtained by the use of a mechanical shaker working at a uniform speed.—J. B. Howell (M.O.H., Hammersmith), *Brit. med. J.*, ii/1934, 883.

The best commercial milk can maintain a standard of less than 10,000 colonies per ml. for at least 24 hours after milking. It maintains its sweetness at room temperature for average of 6·2 days in winter and 3·3 days in summer.—R. S. Williams, *Lancet*, ii/1921, 1386; see also R. T. Hewlett, *ibid.*, i/1922, 102.

Test for Stale, Sour or otherwise Bad Milk

It is known that the addition of hydrogen peroxide to fresh, pure, clean milk produces only slight evolution of oxygen, while in the case of stale, sour milk, or milk containing pus or blood or from animals suffering from inflamed udders, fevers, etc., the test produces a much larger quantity of oxygen and that more rapidly.

Experiments showed the following results:—

(1) With new milk no gas evolution in the first $\frac{1}{2}$ hour. During the next 2 hours about 0·5 ml. evolved.

(2) With sour milk (about 2 days sour) gas evolved at once. After 5 minutes 1 ml. of gas, after 30 minutes 5 ml. In the next two hours a further 1 ml. (The results were obtained using 50 ml. of milk in a Doremus tube.)

Test for Freshness of Milk (Schmidt-Muller). The reagent, which should be freshly boiled each day, consists of 5 ml. saturated alcoholic solution of methylene blue (zinc chloride double salt) with 195 ml. of distilled water. One ml. of the reagent is mixed with 20 ml. of milk, the surface sealed with paraffin, and the test-tube then kept at 45° to 50°. Fresh milk should remain blue for 12 hours or more, reduction of the methylene blue, in the absence of formalin, being due to bacterial contamination. If the solution is decolorised within 1 hour, the organisms certainly exceed 500,000 per ml.—Kenwood.

To determine whether a Sample has been heated:

o-Methylaminophenol sulphate, or **★Ortol** (which is a mixture of this body with quinol and is used in photography) has been used for milk testing. 1 ml. of 1% solution is added to 10 ml. of milk and followed by 1 drop of hydrogen peroxide (10 vols.). Raw milk, or milk that has not been heated above 75°, gives a reddish-pink colour.

Heated Milk. The following modifications may also be used to decide whether a sample has been sterilised or boiled. Mix 3 ml. of milk with 1 ml. freshly prepared 10% hydroquinone solution, and about 15 drops of hydrogen peroxide. A rose colour appears if the milk has not been heated to a high temperature, but otherwise no colour forms, since heat destroys the enzyme responsible for the reaction. The Storch test consists in adding a drop of hydrogen peroxide solution and 2 drops of 2% paraphenylenediamine solution to 5 ml. of milk, and shaking. The liquid becomes indigo-violet, unless the milk has been heated to above 78°, when the colour remains white.—Kenwood.

Neither of these tests is very conclusive. The hydroquinone must be fresh and unoxidised—recrystallise it if necessary.

Cellular Elements present in milk are best stained by Jenner's or May-Grunwald's stain. Sodium chloride of either 0·7%, 0·8% or 0·9% not suitable for washing the cells deposited by centrifuge. Washing with ox serum gave better results, causing the least contraction of the cells of any of the wash liquors tried.—Prof. Hewlett, *Lancet*, i/1915, 855.

Normal milk contains polynuclear and polymorphonuclear leucocytes, which may be mistaken for pus cells; as many as 54,300,000 per ml. have been observed in an apparently normal sample. Mere cell counts do not afford a true criterion of pathological condition of the udder; on the other hand a paucity of cells might also indicate a pathological process.—*Med. Pr.*, i/1914, 457.

All milk contains leucocytes, but do these become converted into pus cells, and how distinguish one from the other? The cell count is increased in milk taken from a cow which is drying off, but the condition is entirely physiological, not pathological. Differential staining should be done by Jenner's method. If an abscess is deep, and has infiltrated the gland, its presence is shown by increased number of phagocytic cells; if acute, the phagocytic activity of the numerous cells is marked; if chronic, and beginning to be shut off by fibrous tissue, the polymorphonuclear cells are less numerous and less sharply defined. The other cells do not appear to be increased in number.—P. C. Varrier-Jones, *Lancet*, ii/1924, 537.

MILK PRESERVATIVES

See also *Food Preservatives*, p. 458.

By the **Public Health (Milk and Cream) Regulations 1912**, which apply to the whole of England and Wales, **the use of preservatives in milk is prohibited**. "No person shall add, or order or permit any other person to add, any preservative substance to milk intended for sale for human consumption, and no person shall sell or expose or offer for sale, or have in his possession for the purpose of sale, any milk to which any preservative substance has been added."

Boric Acid in Milk: Detection (1 in 500 will preserve).

This is detected by evaporating and incinerating at least 10 g. of the milk and acidifying the ash with dilute hydrochloric acid (using litmus). A strip of turmeric paper is now placed in the capsule, so as to be only partly wetted by the liquid. Evaporate to dryness at 100°.

If boron compounds are present, the part immersed in the liquid will turn brownish-red (formation of rosocyanin). On moistening with a drop of caustic soda, green and purple colours will be produced. On re-acidifying with hydrochloric acid, the red colour is restored, and is again changed to green and blue with excess of alkali.

Alternatively make the milk or other substance just alkaline with barium hydroxide solution, evaporate and incinerate. Add a few drops of dilute hydrochloric acid, a saturated solution of oxalic acid and an alcoholic curcumin or turmeric solution, dry on the water-bath and take up with a little alcohol. Boric acid or its salts give intense magenta-red. Reaction is different from, and far more delicate than the ordinary turmeric test.—Kenwood.

The flame test is well-known. Evaporate to dryness, treat the ash with a few drops of strong sulphuric acid, add a little methyl alcohol, and apply a light. The alcohol will burn with green at the edges of the flame (at the moment of ignition more particularly). Boric acid 1 in 5000 is shown with ease by this method using 10 ml. of the sample. It will show even 1 in 8000 but with some uncertainty.

Borax and boric acid cannot be differentiated, as borax alone without the use of sulphuric acid gave the colour even though the ash of the milk alone was alkaline to phenolphthalein. If boron is found, titration of the ash would be the only means of concluding in which form it existed by comparing with an average milk residue boron free.

Determination of Boric Acid, Thomson's Method: To 100 ml. of milk add 1 to 2 g. of sodium hydroxide and evaporate the whole to dryness in a platinum dish. Char thoroughly, avoiding a strong red heat; digest the contents of the dish with about 20 ml. of hot water, then add hydrochloric acid carefully drop by drop until the solution is acid. Transfer the contents of the dish to a 100 ml. flask keeping the volume below 60 ml., add 0·5 g. of solid calcium chloride, and a little phenolphthalein, then 10% caustic soda solution until a slight permanent pink colour is produced. Add 25 ml. of lime water, make

up to 100 ml. and mix well. Filter through a dry filter paper. To 50 ml. of filtrate add N/1 sulphuric acid until the pink colour disappears; add a drop of methyl orange, and more normal acid until the solution is just neutral to methyl orange. Boil for 3 to 4 minutes. Cool, and carefully make the solution neutral to methyl orange with N/10 alkali. Add sufficient neutral glycerin to ensure that a third of the titrated liquid is glycerin, then add a little more phenolphthalein, and titrate with N/10 sodium hydroxide, each ml. of which is equivalent to 0.0062 g. of boric acid.

For a modification of Thomson's method used in the Government Laboratory, see *Analyst*, 1923, 416.

Formaldehyde in Milk: Detection. A teaspoonful will preserve 10 gallons of milk for 3 days in hot weather.

A large addition can be detected by warming, but it is better to distil the milk; the distillate has the odour of formaldehyde, but the preservative is not wholly volatilised even when evaporated to dryness at 100°. In employing colour tests for formaldehyde a notably weaker reaction is obtained when milk containing formaldehyde is distilled and the distillate tested than when water containing the same proportion of formaldehyde is similarly treated.

Schiff's Reagent.—Mix 40 ml. of 0.5% solution of magenta with 250 ml. of water, add 10 ml. of sodium bisulphite solution sp. gr. 1.375, and then 10 ml. of pure strong sulphuric acid; allow to stand for some time, when it will become colourless. It may also be prepared when required for use by adding sufficient of a solution of sulphurous acid to decolourise some of the magenta solution. If the sulphurous acid is added in large excess, traces of formaldehyde will not be indicated. Reddish-violet colour proves presence of formaldehyde. *Other aldehydes, including aromatic aldehydes, also give the reaction.*

It is better to distil as above mentioned or to use Hehner's Test, i.e., purplish-violet ring on layering milk on to strong sulphuric acid; but this is also a group reagent for various aldehyde bodies.

The presence of formaldehyde 1 part in 200,000 can be detected with this test also by the following modification:—

If to the distillate from a sample of milk one drop of a dilute aqueous solution of phenol is added and the mixture poured upon some strong sulphuric acid in a test tube, a bright crimson ring appears.

Phloroglucin Test.—To 5 or 10 ml. of the milk add 5 drops of 1% aqueous phloroglucin solution; shake and add 5 drops of sodium hydroxide solution (30%). Salmon colour (not yellowish tint) indicates addition of formaldehyde. *This test will show 1 of formaldehyde (actual) in 50,000 of milk.*

Rimini's Test.—A satisfactory confirmatory test, being almost specific for formaldehyde. For method of applying see "Formaldehyde in Urine." *This test will show 1 of formaldehyde (actual) in 100,000 of milk.*

Formaldehyde added to foods tends to derange metabolism. Wiley in United States investigated the effects of doses of 100 to 200 milligrammes of formaldehyde (given with milk) on 12 men during 15 days, the total being 2.5 g. to each man. Burning in throat, itching rash, retardation of nitrogen and sulphur metabolism, acceleration of phosphorus metabolism, and loss in bodyweight were observed. Apart from harmfulness as a milk preservative, its use is inadvisable, as in dilute solution it prevents the growth of acid-forming bacteria while not retarding many harmful organisms.

Determination of Formaldehyde. The method of Shrewsbury and Knapp (*Analyst*, 1909, 12) may be used for estimating the amount of formaldehyde in a sample of milk. The following modification has been found to give very satisfactory results.

The reagent (100 ml. of concentrated hydrochloric acid and 0.1 ml. of concentrated nitric acid) becomes yellow very rapidly and masks the colour given by the formaldehyde. To overcome this the acids are added separately to the milk, and the whole then mixed. Add 10 ml. of hydrochloric acid to 5 ml. of the sample contained in a test-tube, then add 1 drop of 5N nitric acid from a pipette, shake and place in a water-bath at 50° for 10 minutes. The tube must not be allowed to touch the bottom of the water-bath. A series of tubes with fresh milk containing added amounts of formaldehyde ranging from less than 1 to, say, 10 parts per million should be treated exactly as above, a blank experiment with the milk used being put on at the same time to ensure its freedom from formaldehyde. After 10 minutes the tubes are removed from the bath, and the intensity of the violet colour in the sample compared with that of the standards.

To prepare standards. Determine the formaldehyde in the formaldehyde solution. Say 40%.

A. Dilute 1 ml. to 100 ml. \therefore 1 ml. of *A* contains $\frac{0.4}{100} = 0.004$ g.

B. Dilute 1 ml. of *A* to 100 ml. \therefore 1 ml. of *B* contains $\frac{0.004}{100} = 0.00004$ g.

Each 0.1 ml. of *B* made up to 5 ml. with milk represents 0.8 parts of formaldehyde per million.

CONDENSED MILK

The changes in the condition of the milk as a result of condensation are profound and not merely caused by deprivation of water.

In the manufacture of sweetened condensed milk, the maximum temperature reached is usually between 80° and 90°, at which temperature it is kept for a few moments. This is not enough to kill many types of bacteria.

Sweetened condensed milk is never sterile; sporing aerobic bacilli have been isolated from 92% of tins and are probably present in every sample—decomposition does not necessarily follow. The “blowing” of tins of sweetened condensed milk is almost invariably due to growth and chemical activities of yeasts but there is no suggestion that these are harmful.

In *unsweetened* condensed milk, the milk is boiled down under reduced pressure. The sealed tins are heated to 110° or 116° for from 30 to 40 minutes, the tins being rotated to increase penetration. About 80% of samples are found to be sterile, the non-sterile containing chiefly spore-bearing aerobes in small numbers, yeasts being of small significance. Decomposition in condensed milk is nearly always due to non-sporing organisms. Longer processing at lower temperature would give results as good as shorter time at higher temperature, without risk of damage to milk.—“Studies in Sweetened and Unsweetened (Evaporated) Condensed Milk,” Food Investigation Board of Dept. of Sci. and Indust. Res., W. G. Savage and R. F. Hunwicke, *Brit. med. J.*, ii/1923, 296; *Lancet*, ii/1923, 529.

The Public Health (Condensed Milk) Regulations, 1923 and 1927 include the following selected articles and rules.

PART I

Article 2. (1) In these Regulations unless the context otherwise requires:—

“Condensed Milk” means milk or skimmed milk which has been concentrated by the removal of part of its water, whether with or without the addition of sugar, and includes the article commonly known as “evaporated milk”, but does not include the article commonly known as “dried milk” or “milk powder”;

“Skimmed Milk” includes separated or machine-skimmed milk;

Percentages shall be calculated by weight.

PART II

Article 4a. Where a tin or other receptacle containing condensed skimmed milk is required by Article 4 of these Regulations to be labelled, no person shall expose or offer for sale such a tin or receptacle in a paper or other wrapper unless such wrapper has printed on the outside thereof the words "unfit for babies," such words being contained within a surrounding line. The type used for the words shall be not less than a quarter of an inch in height, and the printing shall otherwise conform with the rules prescribed for the printing of the same matter on the label affixed to the tin or other receptacle."

The First Schedule

RULES WITH RESPECT TO THE LABELLING OF CONDENSED MILK

1. Every tin or other receptacle containing condensed milk shall bear a label upon which is printed such one of the following declarations as may be applicable or such other declaration substantially to the like effect as may be allowed by the Minister:—

(i) In the case of full cream milk (unsweetened):—

CONDENSED FULL CREAM MILK, UNSWEETENED
THIS TIN CONTAINS THE EQUIVALENT OF
(a) PINTS OF MILK

(ii) In the case of full cream milk (sweetened):—

CONDENSED FULL CREAM MILK, SWEETENED
THIS TIN CONTAINS THE EQUIVALENT OF
(a) PINTS OF MILK, WITH SUGAR ADDED

(iii) In the case of skimmed milk (unsweetened):—

CONDENSED MACHINE-SKIMMED MILK (or CONDENSED
SKIMMED MILK), UNSWEETENED

UNFIT FOR BABIES

THIS TIN CONTAINS THE EQUIVALENT OF
(a) PINTS OF SKIMMED MILK

(iv) In the case of skimmed milk (sweetened):—

CONDENSED MACHINE-SKIMMED MILK (or CONDENSED
SKIMMED MILK), SWEETENED

UNFIT FOR BABIES

THIS TIN CONTAINS THE EQUIVALENT OF
(a) PINTS OF SKIMMED MILK, WITH SUGAR ADDED

2. The declaration shall in each case be completed by inserting at (a) the appropriate number in words and figures, e.g., "one and a half ($1\frac{1}{2}$)," any fraction being expressed as eighths, quarters or a half.

For the purposes of these Rules milk means milk which contains not less than 12.4% of milk solids (including not less than 3.6% of milk fat) and skimmed milk means milk which contains not less than 9% of milk solids other than milk fat.

The Second Schedule

All condensed milk shall contain not less than the appropriate percentages of milk fat and milk solids as specified in the following Table:—

Description of Condensed Milk	Percentage of milk fat	Percentage of all milk solids, including fat
1. Full cream, unsweetened ...	9.0	31.0
2. Full cream, sweetened ...	9.0	31.0
3. Skimmed, unsweetened ...	—	20.0
4. Skimmed, sweetened ...	—	26.0

Standard processes for the examination of Condensed Milk will be found in the *Analyst*, 1927, 402; 1930, 111; and 1932, 630.

The method outlined below has been found to give consistent and satisfactory results.

The determination of the "equivalent pints" of milk as a check upon the statement appearing on the label is an important part of the analysis. The net weight of condensed milk must therefore be known.

Weigh the tin and contents before opening; after opening, transfer the well-mixed contents to a suitable receptacle, wash and dry the empty tin, and weigh.

Prepare a 20% *w/v* solution by mixing 40 g. of condensed milk with water and diluting to 200 ml.

Total Solids. Evaporate 5 ml. of the solution in a platinum dish, and dry in a water-oven to constant weight. Sweetened condensed milks are liable to give somewhat high results unless the solution is mixed with purified ignited sand before evaporation.

Ash. Evaporate 5 or 10 ml. to dryness and ignite at a low red heat.

Protein. Evaporate 5 or 10 ml. of solution for the determination of nitrogen by the Kjeldahl process, using the factor 6.38 to convert to protein.

Fat. An approximate figure may be obtained by the Gerber process, but repeated whirlings are necessary especially with a 20% solution.

More accurately, treat 10 ml. by the Gottlieb method (see *Milk*, page 395) or follow the directions given for this process in the *Analyst*, 1927, 408.

Sugars. Dilute 20 ml. of the 20% solution to 200 ml., to produce a 2% solution.

Lactose. Determine by the volumetric method of Lane and Eynon (*J. Soc. Chem. Ind., Lond.*, 1923, 32-37T.).

The process consists in the titration of Fehling's solution with the use of methylene blue as an *internal* indicator. It has the further advantage that the milk or condensed milk dilution need not be treated by clarifying agents to remove protein and fat.

To 10 ml. of Fehling's solution in a conical flask, add 10 ml. or more of sugar solution; boil for 2 minutes and then titrate the boiling liquid with more sugar solution added at fifteen-second intervals until the copper is nearly all reduced; add 3 to 5 drops of a 1% solution of methylene blue, and continue carefully until the colour of the indicator is discharged. The boiling should be continued uninterruptedly throughout the operation.

A second and more accurate titration may now be made as follows. To 10 ml. of Fehling's solution add nearly the whole of the sugar solution (to within about 1 ml.) before commencing to heat. Bring the mixture to the boil, and boil for 2 minutes; add the indicator and complete the titration within one minute.

The authors give tables of factors for various sugars for 10 ml. and 25 ml. of Fehling's solution, these factors varying slightly according to the volume of titrating liquid used. The tables also allow for the effect of the presence of

sucrose on invert sugar, etc., and in particular on lactose (*J. Soc. chem. Ind. Lond.*, 1927, 434T) for convenience in analysis of condensed milk products.

It is best, however, to standardise the Fehling's solution with known solutions of lactose, etc., under the conditions of experiment, unless the authors' directions are strictly adhered to.

Sucrose. To 50 ml. of the 2% solution add 1 ml. of a 50% solution of citric acid and heat in a thoroughly boiling water-bath for half an hour. Cool, make up the volume to 100 ml. and titrate 10 ml. of Fehling's solution as before. Express the result as sucrose per cent., using the factor found for the Fehling's (approx. 0.0475 g. per 10 ml.), and deduct from it the equivalent in sucrose of the lactose found before inversion.

The percentage of sucrose in the sample is then deducted from that of the total solids to obtain the Total Milk Solids per cent.

Calculation of Equivalent Pints (*Analyst*, 1923, 597).

All tins bear on the label the number of pints of milk to which the contents are equivalent.

By Rule 2 of the regulations, milk contains not less than 12.4% of milk solids (including not less than 3.6% of milk fat).

The specific gravity of such Full Cream Milk is taken as 1.032.

Let *T.M.S.* be the percentage of total milk solids.

„ *S.N.F.* „ „ „ „ solids not fat.

„ *F* „ „ „ „ fat.

„ *W* „ „ weight of contents of the tin in grammes.

For a full cream condensed milk we have:

$$\text{Total milk solids in tin} = T.M.S. \times \frac{W}{100}$$

$$1 \text{ pint} = 20 \text{ fl. oz.} = 20 \times 1.032 = 20.64 \text{ oz. by weight.}$$

$$12.4\% \text{ of this} = 2.559 \text{ oz. of total milk solids in 1 pint of milk.}$$

$$= 2.559 \times 28.35 = 72.55 \text{ grammes.}$$

$$\therefore \text{Equivalent Pints} = \frac{T.M.S. \times W/100}{72.55} = \frac{T.M.S. \times W}{7255}$$

Similarly, equivalent pints are given by the formulæ:—

$$\frac{F \times W}{2106} \text{ and } \frac{S.N.F. \times W}{5149}$$

In the case of a skimmed milk containing not less than 9% of milk solids other than milk fat (sp. gr. 1.036.5) $E.P. = \frac{S.N.F. \times W}{5284}$

Condensed milk should be tested for **poisonous metals**, for boric acid and other preservatives, and for thickening agents such as gelatin and starch.

Stokes' Test may be employed for the detection of **gelatin**: Dissolve mercury in twice its weight of nitric acid, and dilute the resulting solution of mercuric nitrate to 25 times its volume with water. Mix condensed milk diluted with water with an equal volume of this reagent and shake well. Allow to stand for a few minutes, and filter. To the filtrate add a saturated aqueous solution of picric acid in about equal volume. An immediate yellow precipitate is formed if gelatin is present.

DRIED MILK

Abstracts from the Public Health (Dried Milk) Regulations, 1923 and 1927.

“Dried Milk” means milk, partly skimmed milk, or skimmed milk, which has been concentrated to the form of powder or solid by the removal of water;

“Skimmed Milk” includes separated or machine-skimmed milk;

Percentages shall be calculated by weight.

(2) These Regulations apply to dried milk to which no other substance has been added and to the dried milk contained in any powder or solid of which not less than 70% consists of dried milk.

Article 4 lays down the conditions of sale with respect to labelling, and requires the content of milk-fat to be:—

In the case of milk described as dried full cream milk not less than 26%;

In the case of milk described as dried three-quarter cream milk not less than 20%;

In the case of milk described as dried half cream milk not less than 14%; and

In the case of milk described as dried quarter cream milk not less than 8%.

Article 4a. "Where a tin or other receptacle containing dried skimmed milk is required by Article 4 of these Regulations to be labelled, no person shall expose or offer for sale such a tin or receptacle in a paper or other wrapper unless such wrapper has printed on the outside thereof the words 'unfit for babies,' such words being contained within a surrounding line. The type used for the words shall be not less than a quarter of an inch in height and the printing shall otherwise conform with the rules prescribed for the printing of the same matter on the label affixed to the tin or other receptacle."

The Schedule

CHIEF RULES WITH RESPECT TO THE LABELLING OF DRIED MILK

(1) Every tin or other receptacle containing dried milk (other than dried milk which sugar or some other substance has been added) shall bear a label upon which is printed such one of the following declarations as may be applicable or such other declaration substantially to the like effect as may be allowed by the Minister:—

(i) In the case of full cream milk, that is to say, dried milk containing not less than 26% of milk fat:—

DRIED FULL CREAM MILK
THIS TIN CONTAINS THE EQUIVALENT OF
(a) PINTS OF MILK

(ii) In the case of partly skimmed milk, that is to say, dried milk containing not less than 8% but less than 26% of milk fat:—

DRIED PARTLY SKIMMED MILK
[(b) CREAM]
SHOULD NOT BE USED FOR BABIES EXCEPT
UNDER MEDICAL ADVICE
THIS TIN CONTAINS THE EQUIVALENT OF
(a) PINTS OF (b) CREAM MILK

(iii) In the case of skimmed milk, that is to say, dried milk containing less than 8% of milk fat:—

DRIED MACHINE-SKIMMED MILK
(OR DRIED SKIMMED MILK)

UNFIT FOR BABIES

THIS TIN CONTAINS THE EQUIVALENT OF
(a) PINTS OF SKIMMED MILK

(2) The label on any tin or other receptacle containing **dried milk to which sugar or some other substance has been added** shall be in the appropriate form prescribed in subdivision (1) hereof, with the following modifications:—

(i) There shall be added to the heading the word "Sweetened" if the only substance added to the milk is sugar; the word "Modified" if the only substance added is a constituent of milk, and the word "Compounded" in every other case; and

(ii) The words "with (c) added" shall be added to the last sentence in each case, words being inserted at (c) to specify the substance or substances added.

(3) The declaration shall be completed as follows:—

(i) There shall be inserted at (a) the appropriate number in words and figures, e.g., "one-and-a-half ($1\frac{1}{2}$)," any fraction being expressed as eighths, quarters or a half.

(ii) There shall be inserted at (b) the word "Three-quarter" if the percentage of milk fat is not less than 20; "Half" if such percentage is less than 20 but not less than 14; and "Quarter" if such percentage is less than 14 but not less than 8.

(4) For the purposes of this Rule the terms "**Milk**," "**Three-quarter cream milk**," "**Half cream milk**," and "**Quarter cream milk**" mean milk containing not less than the following percentages of milk fat and milk solids, that is to say:—

	Milk Fat	Milk Solids (including fat)
Milk	3·6	12·4
Three-quarter cream milk...	2·7	11·6
Half cream milk	1·8	10·8
Quarter cream milk	·9	9·9

and "**Skimmed milk**" means milk which contains not less than 9% of milk solids other than milk fat.

Formulae for Calculation of Equivalent Pints (*Analyst*, 1924, 471).

W is the total weight of dried milk in grammes, and *F*, *T.M.S.*, and *S.N.F.* are the percentages by weight of fat, total milk solids, and solids-not-fat respectively, in the dried milk.

<i>Milk</i>	Equivalent pints =	$\frac{F \times W}{2107}$ or $\frac{T.M.S. \times W}{7258}$
Three-quarter cream milk	" "	$\frac{F \times W}{1582}$ or $\frac{T.M.S. \times W}{6797}$
Half cream milk	" "	$\frac{F \times W}{1056}$ or $\frac{T.M.S. \times W}{6335}$
Quarter cream milk	" "	$\frac{F \times W}{528}$ or $\frac{T.M.S. \times W}{5811}$
Skimmed milk	" "	$\frac{S.N.F. \times W}{5285}$

Analysis

Moisture (loss at 100°).

Dry 2 g., in a large platinum dish, to constant weight.

Ash

Incinerate the above at a low red heat in a muffle furnace.

Alkalinity of soluble Ash

Wash the ash on to a filter and continue washing with hot water until about 200 ml. of filtrate is collected. Titrate the filtrate with N/10 sulphuric acid, using methyl orange as indicator, and calculate the result as sodium carbonate.

Proteins (Kjeldahl).

Take 1 g. of sample, 20 ml. of concentrated sulphuric acid and 10 g. of potassium sulphate, with a small crystal of copper sulphate. Heat gently in a long-necked flask until frothing ceases and continue heating until clear over a moderate bunsen flame. Cool, add water and pour into a large round-bottomed flask (1½ litre); wash the digestion flask with successive quantities of water making up to a total volume of about 500 ml. Make alkaline with strong caustic soda solution (500 g. per litre) and distil into 50 ml. of N/10 sulphuric acid until all the ammonia has passed over. The condenser tube should dip below the surface of the standard acid in the receiver until near the end of the distillation. Titrate the distillate with N/10 alkali using methyl orange or methyl red as indicator. A blank experiment should be carried out and the amount of acid neutralised deducted from that neutralised in the determination.

Each ml. of N/10 sulphuric acid neutralised by the ammonia in the distillate is equivalent to 0.0014 g. of nitrogen.

Use the factor 6.38 to obtain the equivalent of protein.

Lactose

Dissolve 2 g. of sample as completely as possible, make up volume to 200 ml., mix well, and allow to stand.

Use the decanted liquid to titrate 10 ml. of Fehling's solution by the method of Lane and Eynon (see Condensed Milk).

If desired, a clarified solution for titrating may be prepared as follows:

Rub the dried milk into a thin paste with warm water in a mortar and transfer to a 200 ml. flask. Add 0.5 ml. of 50% citric acid solution, then 5 ml. of alumina cream, warm gently on a water-bath, shake well, make up volume, after cooling, to 200 ml., mix and filter.

To prepare alumina cream, which should be fresh, stir ammonia into a saturated solution of alum until the mixture is alkaline to litmus; then add sufficient of the alum solution to make the mixture just acid to litmus.

Fat: by the Werner-Schmidt method.

Take 1 g. of dried milk, mix thoroughly with 5 to 8 ml. of warm water, add 10 to 15 ml. of strong hydrochloric acid and proceed in the same way as in the case of milk but make at least 4 or 5 extractions with ether.

If any foreign matter appears in the fat, extract the fat with petroleum ether, weigh the residue, and subtract the weight of this from the original weight.

Samples should also be tested for starch, boric acid, salicylic acid, and poisonous metals.

RECONSTITUTED OR SOPHISTICATED MILK

The establishment of the Milk Marketing Board and the elimination of "cut-price" wholesale milk has led to new devices to enhance the value of skimmed milk. Skimmed milk powder is a cheap article of commerce and if dissolved in water and cream added, the resulting solution is not easily distinguishable from natural cow's milk: sold at a shilling a gallon it yields an enormous profit. It is difficult to stop this traffic since it contains the ordinary constituents of cows' milk and passes the ordinary tests of the Food Inspector. The percentage of water and cream can be regulated to a nicety. Whereas, however, the average fat content of genuine cows' milk is about 3.6% the manufacturers of these sophisticated milks are usually content to keep within the legal minimum of 3%; milk which yields consistently on analysis a fat content of 3% or thereabouts is open to grave suspicion. Another device is the mixing of skimmed milk, plus additional cream, with ordinary milk. The addition of 1 gallon of cream to 16 gallons of skimmed milk gives a liquid with fat content just below the minimum standard, but as genuine milk contains fat in excess of this standard the mixture of the two gives a fat content above the legal minimum but less than the average from genuine milk. This gives an additional profit of 9s. 6d. per churn. Present legislation is inadequate to deal with these new activities.—*Brit. med. J.*, ii/1934, 520.

HUMAN MILK

The average composition of human milk is given in Vol I (pp. 579 and 582). Note in particular the high proportion of lactalbumin to casein (Vol. I, p. 579, and this Vol., p. 400, table), and the remarkable difference in mineral matter. *Phosphatide* in human milk is about half that in cow's milk (cf. p. 400). See also *Analyst*, 1928, 78.

In Detroit there is an organisation, with turnover about £2,000 per annum, for the commercial production and distribution of human milk.—*Lancet* 1925, 450.

CREAM

Cream was formerly obtained by skimming from milk which had been allowed to stand overnight. It is now largely prepared by the use of separators depending on centrifugal action. The milk is very effectually deprived of its fat, and the cream is correspondingly richer. There is no standard for the amount of fat, but cream so produced may readily contain 65% or more.

Under the **Milk and Cream Regulations of 1912**, the addition of preservative (which is now prohibited altogether) was not allowed to cream containing less than 35% of fat. The Ministry of Health Report for 1922 stated that "it is fairly generally accepted in this country that cream should contain 40% to 50% of butter fat, with about 5% of non-fatty solids." (Liverseege.) The need for definite standards has long been felt, and it is of particular interest that the standing committee of the Council of Agriculture made special reference to this need in their recent report to the Council (P.W.D.I., *Daily Mail*, 15/13/34). The Committee recommended a scheme previously put forward, suggesting three standards: a 12% cream for breakfast or coffee cream; a 25% standard for fruit cream; and a 50% standard for thick or whipping cream.

The Committee also called for the enforcement of legal standards for the amount and quality of actual cream in all ice-cream sold.

Devonshire or clotted cream may contain 50% to 60% of fat.

Tinned cream usually contains less than 35% of fat. It is often marked "Thick Cream" but "the thickness is due to sterilisation, and not to a good proportion of fat." According to Liverseege ("Adulteration and Analysis of Foods and Drugs") for practical purposes it may be stated that fresh cream contains over 40% of fat, and tinned cream about 23%.

The fat in cream may be determined by the methods employed for milk, about 2 g. of cream being diluted with water. If the apparatus is available the Leffmann-Beam process provides a rapid method, which is described in "Aids to the Analysis of Food and Drugs" (Moor and Partridge).

The Gerber process can also be used for cream. The Werner-Schmidt, Gottlieb, and Adams' methods are all suitable.

Lerrigo points out (*Analyst*, 1928, 488) that many commercial samples of cream contain added water, and refers to the presence and detection of glycerin (*ibid.*, p. 335). A formula for the calculation of added water is given in the *A.O.A.C. Methods of Analysis* (3rd Ed., p. 225), based on the freezing-point determination.

$$W = \frac{\% \text{ serum in cream } (T - T^1)}{T}$$

where W = percentage of added water

T = freezing point of undiluted cream (-0.550°)

T^1 = observed freezing point of given sample

$\% \text{ serum} = 100\% - (\% \text{ fat} + \% \text{ protein})$

If protein has not been determined it may be assumed to be 38% of the solids-not-fat.

The use of **preservatives in cream** is entirely prohibited by the Public Health (Preservatives, etc., in Food) Regulations, 1925, which, in general, came into operation in 1927.

The addition of sucrate of lime, gelatin, starch paste or other thickening substances is also prohibited.

"**Viscogen**" is a form of sucrate of lime which has been used for thickening, its detection depending on the percentage of lime in the ash together with tests for cane sugar.

Starch may be readily detected by iodine solution, and gelatin by means of Stokes' test (see condensed milk).

Artificial Cream Act, 1929. (*Came into force June 1st, 1929.*)

Prohibits the sale of any substance as cream unless it is that portion of natural milk rich in milk fat which is separated by skimming (or otherwise), or artificial cream, in which case the word "*cream*" immediately preceded by the word "*artificial*" must be printed on the container, etc.

Premises must be registered with the Food and Drugs authorities, except when the cream is made for domestic purposes, or used on the same premises for making some other article of food, or where it is supplied only in the unopened receptacles in which it was delivered.

All provisions in previous Acts relating to cream (except as to registration) apply to artificial cream.

"Artificial cream" means an article of food resembling cream and containing no ingredient not derived from milk except water, or any ingredient or material which by virtue of the proviso to sub-section (2) of Section 2 of the Food and Drugs (Adulteration) Act, 1928, may lawfully be contained in an article sold as cream.

The Act does not apply to Northern Ireland.

The following statement is contained in a circular issued by the Ministry with reference to the Act.

"The substance whose sale and manufacture the Act is designed to regulate is a cream substitute which has hitherto been commonly known as reconstituted cream, and is usually prepared by emulsifying butter, dried skimmed milk and water."

Liverseege (*ibid.*) mentions that the Act was rendered necessary by the advertisement, about 1927, of emulsifiers for manufacturing "cream" from the above ingredients.

Richardson, referring to reconstituted cream (*Analyst*, 1928, 334), says it is distinguishable from ordinary cream by taste or use in tea or coffee, and that it is made by combining dried separated milk, saltless butter and water in correct proportions, giving an emulsion containing about 50% of butter-fat.

The first case under the Act came up at Marlborough Street Police Court, on the 13th August 1929, the National Farmers' Union being the prosecuting party, and the charge being the selling of an article described as cream without the word "cream" being immediately preceded by the word "artificial." The defence maintained that the prosecution could only be undertaken by the local authority, but the magistrate ruled otherwise and inflicted a fine of £10 and costs, stating that the labels used by the defendants were misleading.—*Daily Mail*, Aug. 14, 1929.

An appeal against this conviction was allowed on the ground that the action was not brought by a body entitled to take proceedings under the Act.—*Brit. Food J.*, October, 1929.

Legal proceedings have been taken under the Act against several firms for use of descriptive terms such as "**Cream Sandwiches**," "**Cream Cakes**," "**Devonshire Cream Cakes**," "**Cornish Cream Cakes**," "**Pure Cream Buns**," etc., for articles not containing genuine cream derived from cows' milk. The varying results are recorded in detailed reports in the issues of the *British Food Journal* from 1929 to the present time.

Convictions are recorded in the *Analyst* (1935, 174) for the sale of "**Real Cream Tarts**," "**Real Cream Eclairs**," etc., in which the filling resembled real cream but contained fat other than milk-fat.

Bacterial content. Thirty-six samples of ice cream bought in a London district during the summer of 1934 were examined with the following results:—

4	samples contained over 1 million per ml. (including the above case)
2	„ „ less than „ „ but more than 500,000
10	„ „ „ 500,000 „ „ „ 100,000

Coliform bacilli were not found in 18 cases (1/100th ml.)

„ „ „ present „ 3 cases in 1/100th ml.

15	1/1000th ml.
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6 of these cases in 1/10,000th ml.

" " " " " 3 " " " 1/100,000th ml.

the enumerations in these last three cases being 925,000; 308,000; 4,600,000.

On the whole the above figures may be said to compare favourably with those quoted in the last edition and elsewhere, which may be attributable to improved methods of manufacture and storage.

The methods of examination and the media used corresponded with those prescribed by the Ministry of Health for Graded Milks, see p. 422.

The general examination of butter includes determination of the proportions of water, curd, salt, and fat in the sample, followed by a special examination of the clarified fat for the presence of foreign fats or oils.

(i) **Water:**—Heat 5 g. in an air-oven to 110°. The loss must not exceed 16%; if more, suspect careless making or intentional adulteration. See *Food and Drugs (Adulteration) Act, 1928*

(ii) **Curd and Salt:**—Melt the residue of (i) and treat with 10 ml. of ether, filter through a tared filter, repeat the process and wash until all ether-soluble matter is removed, dry the residue, and weigh: the residue consists of curd and salt.

(iii) **Ash:**—Ignite residue from (ii) and weigh. Should be wholly salt; confirm this by titration with standard silver nitrate solution.

(iv) **Fat:**—Should be taken by difference by subtracting the sum of percentages of water, curd and salt from 100.

(v) **Detection of Foreign Fats:**—Butter fat has certain characteristics which help to distinguish it from other fats. Some of its constituents are of lower molecular weight than those found in other animal and vegetable fats and oils. When the fat is saponified, the glycerides composing it yield glycerol and fatty acids which are liberated in acid solution. They have the marked odour of butyric acid, the most characteristic component of butter, and contain a larger proportion than usual of fatty acids soluble in water and volatile in steam, and this property is made use of in analysis for the detection of foreign fats. Besides butyric acid there are present caproic, caprylic, capric, lauric, myristic, palmitic, stearic and oleic acids, which may occur as simple glyceryl esters such as triolein or glyceryl trioleate, or as mixed esters in which more than one fatty acid radicle is combined.

in the molecule of the glyceryl compound, for example, palmito-stearin. Compounds of oleic, palmitic and stearic acids preponderate in animal fats such as lard, tallow and beef-fat, and in varying proportions in most vegetable fats and oils. Coconut and palm-kernel oils are intermediate in character but yield considerably less soluble volatile acids, and an increased proportion of insoluble volatile acids in comparison with butter-fat. The introduction of these and other oils (see Margarine) considerably increased the difficulty of detecting adulteration. Formerly distillation of the fatty acids by the Reichert method, determinations of iodine values and other chemical constants, and physical characters such as solubility or miscibility and the refractive index all furnished clear indications of the presence of foreign fats, usually oleo-margarine. But, by skilful admixture of various fats and oils now available with butter of a high Reichert value, blends may be produced which answer many of the tests for genuine butter.

At the present day the combined Reichert-Polenské-Kirschner processes form the most important means relied on for the detection and estimation of the amount of adulteration.

The **Reichert** process has undergone modification in detail by Meissl, Wollny, Leffman and Beam and others to its present form.

The values obtained for 5 grammes of butter-fat are known as the Reichert-Meissl or Reichert-Wollny values, the saponification being carried out with the glycerol-soda solution, introduced by Leffmann and Beam, instead of alcohol, the purpose of the Polenské determination which follows.

Carried out under standard conditions of method and apparatus, the combined process yields:—

- (i) The **Reichert-Meissl Value** which is a measure of the soluble volatile fatty acids obtained from 5 grammes of fat.
- (ii) The **Polenské Value** which is similarly a measure of the insoluble volatile fatty acids.
- (iii) The **Kirschner Value** which practically measures the butyric acid in the sample.

The following solutions are required:—

- (a) A strong solution of sodium hydroxide (1 and 1) prepared by dissolving 10 g. of sodium hydroxide in 100 ml. of water and allowing to stand until clear, the solution being protected from access of CO_2 .
- (b) Glycerol-soda: made by mixing 20 ml. of the sodium hydroxide solution with 180 ml. of glycerin.
- (c) Dilute sulphuric acid: made by carefully adding 200 ml. of concentrated acid to 800 ml. of water.

Reichert-Meissl or Reichert-Wollny Value. Saponify 5 g. of the clear melted butter-fat in a 300 ml. flask by heating with 20 ml. of the glycerol-soda solution; allow to cool somewhat and add, cautiously at first, 135 ml. of hot water which has been well boiled. Add a few fragments of pumice, and then acidify with 6 ml. of the dilute sulphuric acid. Attach the flask to a standard distillation apparatus (*Methods of Analysis, A.O.A.C.*, 3rd Edn., p. 323; *Analyst*, 1904, 5) and distil so that 110 ml. of the distillate is collected in about 20 minutes. Remove the 110 ml. receiving flask and place a measuring cylinder (or other suitable vessel) under the condenser. Cool the distillate to 15° , mix gently, and pour the 110 ml. through a dry filter rejecting the first few millilitres. Treat 100 ml. with N/10 soda using phenolphthalein as indicator. Set aside the treated liquid for the Kirschner determination.

From the number of millilitres of N/10 soda required by the 100 ml. of distillate, deduct the amount required in a blank experiment conducted with the reagents but without the fat, then add on one-tenth (110 ml. having been distilled) to obtain the Reichert-Meissl value.

Polenské Value. Wash the condenser tube, measuring cylinder and 110 ml. flask with small quantities of water, 18 ml. to 20 ml. in all, and pass the washing through the filter used in the Reichert process. Reject the filtrate. Dissolve the water-insoluble acids by passing three successive 15 ml. portions of neutral alcohol through the condenser, cylinder, 110 ml. flask and filter paper. Titrate the combined alcoholic washings with N/10 soda using phenolphthalein as before. The number of millilitres required is the insoluble volatile acid or Polenské value.

Kirschner Value. Add 0.5 g. of finely powdered silver sulphate to the titrated liquid from the Reichert determination, and shake frequently during at least an hour. Filter and transfer 100 ml. to a 300 ml. flask, add 10 ml. of diluted sulphuric acid (25 ml. per litre), 35 ml. of water, a little pumice, and distil in the standard apparatus, collecting 110 ml. in about 20 minutes. Titrate 100 ml. with N/10 soda, deduct the result of a blank experiment, and calculate the Kirschner value from the following equation.

$$K = \frac{110}{100} \times \frac{110A}{100} \times \frac{100 + B}{100} = \frac{121A(100 + B)}{10,000}$$

where A = corrected Kirschner titration

B = number of millilitres of N/10 alkali required to neutralise 100 ml. of Reichert-Meissl distillate.

The Kirschner value is of importance in the detection and *estimation of butter-fat in margarine*, which must not contain more than 10%.

In a paper on the examination of New Zealand butter-fat by Hilditch and Jones (*Analyst*, 1929, 75) it is stated that "the relation of the observed butyric acid content to that calculated on the assumption that the Kirschner value is a simple measure of the butyric acid would seem to show that the latter registers in terms of butyric acid about 15% to 20% more than is actually present in the fat."

The possibility that the Kirschner value included caproic acid was mentioned in the discussion.

Reichert values for genuine butter-fat usually lie between 24 and 32, Polenské values range from about 1.4 to 3.5 and the Kirschner values from 20 to 26. These values are roughly proportional, a high Reichert being accompanied by high Polenské and Kirschner, whilst low values for one are associated in genuine samples with low values for the others.

The limits given above for the Reichert value are frequently exceeded and, in particular, values of 23 and lower are met with (in Irish, Russian and Siberian butters) which are not necessarily suspicious, especially if the Polenské and Kirschner correspond.

Coconut oil gives a Reichert-Meissl value of 6 to 8, and a Polenské of 15 to 20.

It thus contains an appreciable amount of volatile fatty acids soluble in water though much less than butter-fat.

The high Polenské representing volatile insoluble acids is characteristic of both coconut and *palm kernel oil*, distinguishing them from butter and from other vegetable oils and fats. It is said to be due mainly to myristic and lauric acids (Winton: *Structure and Composition of Foods*, Vol. I, 384), other acids found being palmitic, stearic, oleic and caprylic, but not caproic and capric.

As in butter, it appears also in coconut oil that the esters are not necessarily simple triglycerides of one acid, but that two or three acid radicles may occur in one molecule, e.g., caprylo-lauro myristin and myristo dilaurin.

Various formulæ have been proposed for calculating the approximate composition of adulterated samples of butter from the analytical data. Different formulæ have to be used according to whether coconut and palm kernel oil are present or not.

Much work has also been done on the subject of the variation of the analytical figures obtained with known mixtures of butter and coconut oil from the calculated figures.

Experience in interpretation of the results of analysis is of great importance in this as in other branches of chemical work. A valuable guide to a decision may be furnished by the preparation and analysis of a series (or rather two series) of mixtures of butter-fat (a) of high and (b) of low Reichert values with different percentages of coconut oil and/or other possible constituents.

The possession of such analytical results of known mixtures provides a very useful check upon the conclusions arrived at by other means.

Vitamin Content of Butter. Australian and New Zealand butters sold in this country have as high a vitamin A and D content as butters produced in Great Britain and elsewhere in Europe. There is a considerable fall in the vitamin content of British butter during the winter, from stall-fed cows, but the vitamin content of Australian butter shows little decline. Cold storage has little effect on vitamin content—even after two years cold storage little loss can be detected; neither is it affected by the racial origin of the herds.—*Spec. Rep. Ser. med. Res. Coun., Lond., No. 175, 1932; Brit. med. J., ii/1932, 1024.*

Vitamin D of butter is destroyed by boiling with alcoholic potash. In this respect it is different from the vitamin D of irradiated ergosterol and of cod-liver oil.—S. G. Kon and R. G. Booth, *Biochem. J.*, 1933, 1302.

Tuberculous Butter.—Persistence of tubercle bacilli in butter from tuberculous milk. Milk from tuberculous cows was made into butter and guinea-pig inoculations were made from the material. The milks were shown to contain tubercle bacilli and one sample of butter made from naturally ripened milk contained it. The butter made in other ways from this milk was similarly infected. The question of persistence of the organism in both salted and unsalted butter after ice storage is under further investigation.—H. A. Cookson, *Brit. med. J.*, ii/1926, 637.

The conclusions of the previous writer arrived at in U.S.A. in 1910. "Tubercle bacilli will retain their vitality and virulence while in butter, under common market conditions, for at least 5 months."—S. G. Moore, *Brit. med. J.*, ii/1926, 855.

Biological Detection of Tubercle Bacilli in Butter. From 60 g. to 100 g. of butter is melted at 40° in 150 ml. distilled water in a beaker. This is pumped through a cream-making machine into a centrifuge tube and centrifuged at 3000 revolutions per minute for 30 minutes. The cream is removed, the supernatant liquid poured off, the deposit suspended in 5 ml. of saline and inoculated subcutaneously in equal amounts into the artero-internal aspects of the right thigh of each of two guinea-pigs, the inguinal glands having been previously squeezed after the method of Block. The animals are killed after a month and examined for tuberculosis arising from the site of inoculation. Of 40 samples of Danish, New Zealand and Australian butters examined the organism was found in one of the Danish samples.—J. W. Eddington, *Lancet*, ii/1934, 81.

MARGARINE

For recent relative legislation see Food and Drugs (Adulteration) Act, 1928, postea.

Materials used include beef fat, lard, cottonseed oil, cottonseed stearin, arachis, olive, coconut, palm kernel, maize and sunflower oils. Fats used here are chiefly the vegetable coconut and palm kernel oil. The Reichert-Meissl or Reichert-Wollny numbers give the relative proportion of the lower numbers of the series of fatty acids. Coconut and palm kernel contain a larger proportion than most vegetable fats of the esters of these fatty acids. The R.M. number for butter is 25 to 30, and any butter giving a lower figure is suspicious.—*Brit. med. J.*, i/1915, 855. In support of margarine; hygienic manufacture.—*Brit. med. J.*, i/1915, 1032.

Soya bean, coconut and cottonseed oils probably the principal ones now used. "Illipe Butter" covers a large variety of solid vegetable fats of totally diverse composition, and the term has now lost any special significance. Vegetable substitutes are replacing lard (which is a common constituent), e.g., refined shea nut oil and shea nut "oleine." Mutton fat seldom used owing to flavour.—*Chem. & Drugg.*, ii/1927, 472.

Maize Oil. Well refined maize oil used as salad oil (usually mixed with edible cottonseed and other oils); also used in margarine manufacture. Non-edible maize oil used for making soft soap, and lower qualities for burning oil. Iodine value, 115 to 125; m.p. of fatty acids, 18° to 20°.—*Chem. & Drugg.*, ii/1927, 412.

Vegetable oils to the extent of 40% to 90% of the total fat were found in 15 samples—in most cases it was coconut oil.—*Brit. med. J.*, ii/1911, 959, 1336.

The Vitamin Content of Margarine.

Four brands of margarine, bought in the open market, in which a vitamin concentrate is incorporated during manufacture, shown by animal experiments to be equal to the best summer butter in vitamin A and D content. No sample of butter bought in the open market was found to have a higher vitamin D content than these margarines.—K. H. Coward, *Lancet*, ii/1928, 727.

A Committee of the Institute of Hygiene has submitted the following recommendations with regard to *the properties of a good margarine*. It must be made from pure ingredients and contain vitamins A and D in amounts equal to those found in samples of best summer butter. It should not contain more than 10% of water and should be free from preservatives other than salt. It should be coloured with carotene and not aniline dye, and should contain butter fat up to 10% of total fat.—*Lancet*, i/1932, 1263.

FOOD AND DRUGS (ADULTERATION) ACT, 1928.

Part I.—

(1) No person to mix, colour, stain, or powder any article of food with an ingredient injurious to health, or any drug with an ingredient injuriously affecting the quality or potency of the drug, and no person to sell food or drugs so treated.

(2) No person to sell an article of food or a drug not of the nature, substance, or quality demanded by the purchaser, except where an ingredient not injurious to health has been added as a preservative and not to increase the bulk or conceal inferior quality, or where the food or drug is the subject of a patent, or is unavoidably mixed with extraneous matter, or where, in the case of whisky, brandy, rum, or gin, it is not adulterated other than by the addition of water and is not reduced to more than 35° U.P.

(4) No person is guilty of an offence if the food or drug is distinctly labelled to the effect that it is mixed with an ingredient non-injurious to health.

Part II.—

(6) It is unlawful to manufacture or sell margarine containing more than 10% of fat derived from milk. Every package or parcel containing margarine, margarine-cheese, or milk-blended butter must be clearly marked with the words "*Margarine*," "*Margarine-Cheese*" or "*Milk-blended Butter*."

(8) All *factories* of margarine, margarine-cheese, milk-blended butter or trade butter and all wholesale dealers in these *must be registered* with the Food and Drugs Authority.

(9) Occupiers of such factories and wholesale dealers must keep a register showing the quantity and destination of each consignment, and the register must be open to inspection by Officers of the Ministry of Agriculture and Fisheries.

(10) If any substance intended for the adulteration of butter is found in a butter factory the occupier shall be guilty of an offence.

(11) Any person selling or consigning *butter or margarine containing more than 16% water* (whether due to adulteration or not), or milk-blended butter containing more than 24% water shall be guilty of an offence.

(12) *Prohibits the importation* of margarine, or margarine-cheese, adulterated or impoverished milk or cream, condensed, separated, or skimmed milk, any adulterated or impoverished article of food, unless conspicuously labelled as indicated in the Act, also butter and margarine containing more than 16% water and milk-blended butter containing more than 24% water, and any of these latter containing prohibited preservatives or preservatives in excess of the Act.

For the purposes of the Act a food is deemed adulterated or impoverished if it has been mixed with any other substance or if any part has been abstracted so as to affect injuriously its nature, substance, or quality, but it is not deemed adulterated by reason only of addition of preservatives or colouring matter of such a nature and in such quantity as not to render the article injurious to health.

PART III.—

This deals with Administration of the Act. (18). A person purchasing a sample of any article with the intention of submitting it to analysis must notify the seller or his agent of this intention and must then and there divide the sample into three parts, each to be marked and sealed, one to be given to the seller, one retained for future comparison, and one submitted to the analyst. (25) Every public analyst to report quarterly to the authority appointing him as to the number of articles analysed by him under the Act, the result of each analysis, and the sum paid him in respect of it.

Part IV.—This deals with Legal Proceedings.

Part V.—*Miscellaneous.* (35) The act applies also to Scotland and to Northern Ireland subject to small modifications.

Came into operation 1st January, 1929. The Fourth Schedule to the Act repeals the Sale of Food and Drugs Acts 1875-1899 and 1927 with certain exceptions, as follows:—

ENACTMENTS REPEALED

(Except (Sect. 37) as regards Analyses, Orders, etc., under the old Acts)

Session and Chapter	Short Title	Extent of Repeal
38 & 39 Vict. c. 63	The Sale of Food and Drugs Act, 1875	The whole Act, except secs. 30, 31 & 36*.
42 & 43 Vict. c. 30	The Sale of Food and Drugs Act Amend. Act., 1879	The whole Act.
50 & 51 Vict. c. 29	The Margarine Act, 1887	The whole Act.
55 & 56 Vict. c. 55	The Burgh Police (Scotland) Act, 1892	In sec. 432 the words "under the Sale of Food and Drugs Act, 1875, and also."
62 & 63 Vict. c. 51	The Sale of Food and Drugs Act, 1899	The whole Act.
7 Edw. 7. c. 21	Butter and Marg. Act, 1907	The whole Act.
4 & 5 Geo. 5. c. 46	The Milk and Dairies (Scotland) Act, 1914	Section twenty-seven.
5 & 6 Geo. 5. c. 66	The Milk and Dairies (Consolidation) Act, 1915	Section nine and the Third Schedule.
11 & 12 Geo. 5. c. 32	The Finance Act, 1921	Section twenty-three.
11 & 12 Geo. 5. c. 42	The Licensing Act, 1921	Section ten.
17 & 18 Geo. 5. c. 5	Sale Food Drugs Act, 1927	The whole Act.

*These Sections refer to the inspection, analysis and destruction of *Tea*.

Report of the Departmental Committee on the Composition and Description of Food (Cmd. 4564, April 1934). The committee consider it desirable that the law should be altered so that standards may be set or declarations of composition required for foods other than milk.

JAM

The Ministry of Agriculture has established a Standard for jam of superior quality prepared from fresh fruit grown in the United Kingdom and in the **Agricultural Products (Grading and Marking) (Jam) Regulations, 1934**, prescribes a grade designation as follows:—

“Select (Fresh Fruit) Preserve”

“and the quality indicated by such grade designation shall be deemed to be as defined in the First Schedule hereto.”

This Schedule, the only one at present, is reproduced here.

SCHEDULE I

JAM MANUFACTURED IN ENGLAND AND WALES FROM FRUIT GROWN IN THE UNITED KINGDOM: DEFINITIONS OF QUALITY OF SELECT (FRESH FRUIT) PRESERVE

Definitions of Quality				
Grade Designation	Special Characteristics		General Characteristics	
	Variety of Preserve	Minimum Quantity of Fruit used per 100 lb. of finished Preserve	Fruit	Sweetening Material
Select (Fresh Fruit) Preserve	Blackcurrant Redcurrant Green gooseberry Red gooseberry Victoria plum Green or golden plum Red plum Damson Greengage Quince	lb. 40 45 45 50 50 45 50 50 50 40	The preserve shall be a single fruit jam made in England and Wales from fresh fruit grown in the United Kingdom. The fruit used shall be fresh fruit which has not been subjected to any process of preservation prior to its use in the manufacture of the preserve and shall be sound, clean and free from fermentation and moulds.	All sugar used shall be crystallized refined white sugar or white rose syrup. The preserve shall contain no added sweetening material other than sucrose or invert sugar.
	Strawberry Raspberry Blackberry Loganberry Cherry	55 50 50 50 55		The preserve shall contain no added colouring or flavoured preservative, but may contain an added quantity of any other substance which occurs as a natural constituent of the fruit.
			Soluble Solids	Other Materials
			The preserve shall contain no added colouring or flavoured preservative, no added pectin or other setting materials and no added acids.	The preserve shall contain no added colouring or flavoured preservative, but may contain an added quantity of any other substance which occurs as a natural constituent of the fruit.
			General	
			The preserve shall be sound and of good keeping quality without objectionable flavour,* and shall be free from foreign matter, undeveloped fruit, fermentation, crystallization or mould growth.	

It contains fifteen varieties of preserve, and differs from the Schedule contained in the Regulations of 1933 in that five of the preserves are separated from the remainder on the point of the introduction of other materials.

In common with the other preserves they shall contain no added colouring or flavouring material or preservative, but they may contain an added quantity of any other substance which occurs as a natural constituent of the fruit. This is in order to secure a "satisfactory set," and thus admits of the introduction of pectin; and also acids where a deficiency of these occurs.

These are all single-fruit preserves, and it is laid down that they shall be made from sound and clean fresh fruit and pure sugar, and shall contain no added sweetening material other than sucrose or invert sugar.

This **National Mark Scheme for Jam** is designed to encourage the production of jam of standard quality from home-grown fruit. Large quantities of fruit of varieties grown in this country are imported for manufacture into jam. They come in as whole fruit and pulp, canned or preserved, or as dried fruit (also preserved), and the purchaser is not usually in a position to distinguish between jam made from these and the product of home-grown fruit.

"It is estimated that some 40% of the jam made in this country—other than that made from varieties of fruit which cannot be grown here commercially—is produced from imported fruit or pulp."—Ministry of Agriculture, Marketing Leaflet, No. 36.

Important features of the Scheme are the efforts made to ensure that the jam may be readily identified, and the provision, under Government control, of a guarantee both of the origin of the product, and of the observance of standards of quality officially defined. It includes a system of inspection supported by systematic and regular analyses.

STANDARD FOR JAM

The need for improvement in the conditions of manufacture and the quality of jam has been felt for some time, and standards were adopted in 1930 by the Food Manufacturers' Federation in consultation with the Society of Public Analysts (*Analyst*, November, 1930).

These cover single-fruit and mixed jams, and prescribe for first and second qualities, to be labelled "**Full Fruit Standard**" and "**Lower Fruit Standard**" respectively, with a guarantee on the label, and each manufacturer is to undertake to conform to the standards before he shall be entitled to use the descriptions.

In the preparation of these jams, of course, fruit other than fresh may be used, the percentage of soluble solids—68·5—is in agreement with that required by the Ministry of Agriculture, but the minimum quantity of fruit required to be used in making 100 lb. of finished jam is lower, ranging, for single-fruit jams, from 30 to 45 lbs., while the Ministry requires 40 to 55 lbs., according to the variety of fruit.

The use of glucose is not prohibited, and added fruit juice and pectin may be present, without declaration in the case of first quality jams. The use of citric, tartaric and malic acids and of "permitted" artificial colouring matter is also allowed without declaration.

Tables are given of the minimum percentages of fruit-content in mixed jams, the minimum of each named fruit being given by the figures in brackets; thus for first quality mixed jam, whose total minimum in every case is 40%:—

			Fruit content per cent.
Strawberry and gooseberry	40 (20/20)
Gooseberry and strawberry	40 (30/10)

the name of the fruit forming the larger content appearing first, where the proportions are not equal.

20% is the minimum fruit content for second quality jams, whether single-fruit or mixed.

In addition to the above there are very varied regulations in force in other countries to some of which British jams may be exported. These regulations are discussed and arranged in comparative tables by C. L. Hinton in *A Summary of Food Laws and Regulations* (Nema Press).

ANALYSIS OF JAM

It will be seen from the standards referred to, and the schedule reproduced above, that an examination of jam includes determination of the total soluble solids, and of the proportion of fruit used in the preparation of the sample.

The latter is a difficult problem the solution of which depends largely on a knowledge of the amounts of insoluble solids, acids and pectin contained in the fruit used, and these vary rather widely in different samples of the same fruit. But by consideration of all three figures a fairly good approximation may be arrived at in the case of single-fruit jams.

A paper on the composition of fruits as used for jam manufacture has been published (*Analyst*, 1931, 35) by T. Macara, Director of Research for the British Association of Research for the Jam and other Trades. In it appear the tabulated results of a large number of analyses of different kinds of fruit carried out during the preceding seven years. Details are given of the methods employed; emphasis is laid on the preliminary preparation and mixing of the sample, and on the importance of analysing a jam in a similar manner to that used for the fruits if the data given for the fruit are to be used in interpreting the results of the jam analysis.

The following directions for the analysis of jam, therefore, conform in outline to the description of the methods employed for the fruit when it is a question of obtaining comparative figures.

Preparation of a 20% Extract

Mix the sample thoroughly in a mortar or small mincer (stones having been removed and their proportion noted). Boil 50 g. moderately with 200 ml. of water for one hour, maintaining the volume during boiling. Cool and make up to 250 ml. Mix well and strain or filter.

Soluble Solids may be obtained from the specific gravity or the refractive index (by immersion refractometer) of the 20% extract, the percentage of solids being calculated by means of the appropriate sugar factors (*Analyst*, 1931, 395).

The soluble solids, of course, are required to conform to the standard of 68.5% when determined by refractometer reading in the cold (20° adopted), uncorrected for insoluble solids.

They may be determined directly on the sample which has been thoroughly mixed, other types of refractometer being used. A table prepared by Hinton (loc. cit.) gives the percentages of sugar corresponding to the refractive index or butyrefractometer number observed, for use in the absence of a refractometer reading sugar percentages directly.

In the case of the immersion refractometer, which also has an arbitrary scale the refractive indices may be found by reference to a table in Leach's *Food Inspection and Analysis* (4th Edn., p. 102).

The very small amount of substance used renders it necessary that great care should be taken in mixing the sample if erroneous results are to be avoided.

Sugars. Treat a portion of the extract with lead subacetate, make up to a suitable volume, filter and remove excess of lead from part of the filtrate by means of sodium phosphate. Invert the clean filtrate at 60° with hydrochloric acid, cool, neutralise with sodium hydroxide, and determine the reducing sugar by copper reduction (either gravimetrically or by the volumetric method of Lane and Eynon—see this volume, p. 429).

Acidity. Dilute 50 ml. with several hundred millilitres of water, and titrate with N/10 sodium hydroxide, using phenolphthalein solution as indicator. Deduct any blank obtained by titrating an equal volume of water, and express the result as crystalline citric acid or, in the case of apples, as malic acid.

Pectin (*Spec. Rep. Food Invest. Bd., Lond., No. 33, 73*); cf. Method of Carré and Haynes, *Biochem. J.*, 1922, 63).

Take sufficient of the **filtered** extract to yield from 0.02 g. to 0.03 g. of calcium pectate; neutralise, and dilute so that after addition of all reagents the total volume measures about 500 ml. Add 100 ml. of N/10 sodium hydroxide and allow to stand at least an hour, preferably overnight. Add 50 ml. of N/1 acetic acid, and after 5 minutes, 50 ml. of M/1 calcium chloride. Allow to stand for one hour, boil for a few minutes and filter through a large fluted filter paper. Wash with boiling water until the filtrate is free from chloride, wash the precipitate back into the beaker, boil and filter again. Repeat unless the filtrate gives no indication of chloride. Filter through a Gooch crucible or tared filter, and dry at 100° to constant weight.

In the foregoing method the pectin is determined as calcium pectate. The following points from pages 27 and 28 of the report with reference to pectin and its related compounds may be of interest here.

- (1) An insoluble pectic compound occurs in unripe fruits and other plant tissues, and is generally described as pectose or protopectin. **Pectose** may be regarded as a pectin-cellulose complex with a constitution analogous to that of the glycosides.

- (2) **Pectin** is a neutral methoxy ester of pectic acid and contains 11.76% of methyl alcohol.

Between pectin and pectic acid are intermediate forms which exhibit increasing acidic properties with a decrease in their content of methyl alcohol.

These intermediate forms are classed together as **pectinic acids** to distinguish them from true pectin.

- (3) **Pectic acid** may be regarded as the basal molecule of pectin, and is a complex galacturonic acid combined with arabinose and galactose.

In pectin the carboxyl groups of the galacturonic acid are replaced by methyl alcohol, and both methyl alcohol groups and carboxyl groups are present in pectinic acids.

- (4) Pectin can be converted quantitatively into calcium pectate, whereby the methoxy groups are removed by hydrolysis and the free carboxyl groups are subsequently replaced by calcium. **Calcium pectate** is a definite chemical compound with an ash content found by experiment to be 7.62% of calcium (Carré and Haynes, 1922).

- (5) The formula of pectin may be provisionally accepted as $C_{39}H_{59}O_{33}$, and the basal molecule, pectic acid, will therefore be $C_{35}H_{50}O_{33}$, with a theoretical calcium content of 7.66%.

Pectin is the only member of the group of pectic compounds which is of commercial importance in the jam and jelly industries.

The pectin is extracted from plant material rich in pectic substances, such as citrus fruits, beets, apples, turnips, etc.

The minced material is either subjected to the action of superheated steam or is heated in water under pressure. Some investigators have recommended extraction of the pectin with dilute acid.

In all cases, however, the underlying principle is the same, viz., the hydrolysis of pectose with the production of pectin.

Pectin for commercial use is prepared either in the form of concentrated extracts, or as a dry powder obtained by precipitating the aqueous extract with alcohol.

The relation of pectin to jelly formation is discussed in the report, and also the legitimate use of tasteless and colourless pectin prepared from fruits, such as apple, to "supplement fruits required for jam making which are naturally deficient in pectin."

Certainly this procedure would seem to be a distinct advance on the older method of introducing foreign ingredients such as gelatin and agar.

Insoluble Matter. Take 10 g. of the well-mixed minced material, dilute with 100 ml. of water and boil for 30 minutes, pour on to a tared filter, return the residue to the beaker and boil with more water. Finally wash on the filter with boiling water and dry in an oven at 105°.

The figures used in calculating the proportion of fruit in jam are those for insoluble solids, acidity and pectin. The *Analyst*, 1931, 39, gives a table of extreme and average figures for various fruits. It is suggested that the composition should first be calculated with the use of the average figures. If the jam falls below the standard, the three minima should be used. If it is still below there is little doubt that it was not made with the standard weight of fruit. A warning is added, however, with regard to the difficulty of ensuring even distribution of the fruit and therefore recommending where possible, the examination of more than one jar. Where more than one jar from a boiling is tested it is found that the insoluble solids may vary somewhat widely, but acid and pectin remain much the same, especially the acid.

The acid figure will generally give a fair indication of the composition, except when acid has been added.

Mixed jams present greater difficulties, and call for further methods such as counting and identifying seeds, and for a general microscopical examination, which should be made in every case.

A dissecting microscope is frequently useful for enumerating characteristic elements which do not require high magnification for their detection.

Under the title "The Composition of Fruit," Lampitt and Hughes publish tables of analyses of fresh fruit, covering a period of 2 years (*Analyst*, 1928, 32). Maximum, minimum and average results are given for total solids, total sugars (as invert sugar), pectin (*A.O.A.C.* method), and insoluble solids. These are of value for reference and comparison, allowing for any variations due to possible differences in the methods of determination.

Hughes and Maunsell have published further tables (*Analyst*, 1934, 231), in which another figure, the non-sugar solids, is included, the authors considering it useful in calculating the amount of fruit in canned fruit, jam, etc.

In the same number, p. 248, Hinton advocates the examination of fruit and jam by lead precipitation for the same purpose.

Examination for Glucose, Saccharin and Preservatives

Jams require examination also for the presence of glucose, saccharin, thickening agents, such as gelatin and agar, for preservatives, colouring matter, etc.

Glucose. A simple polarimetric test for the detection of glucose is given by Judd Lewis (*Analyst*, 1930, 384) who points out that the specific rotation of the inverted extract of all fruit juices is approximately -20° .

With 10% of glucose present a specific rotation of $+1.2^\circ$ was obtained. A positive or reduced negative result therefore indicates glucose.

Saccharin has been found in jam as a sweetening agent. It may be extracted by an ether light petroleum mixture from a solution acidified with dilute sulphuric acid, and, after removal of the volatile solvent, detected by its sweet taste, and by fusing with caustic alkali, acidifying and testing for salicylic acid by weak ferric chloride or iron alum solution. Salicylic acid itself is assumed absent. If not it can be removed by oxidising with alkaline permanganate before the fusion with sodium hydroxide. Benzoic acid, if present, can be removed by sublimation at 100° .

Preservatives: Sulphur Dioxide. The only preservative permitted in jams is sulphur dioxide and its compounds which are allowed in ordinary jams to the extent of 40 parts of sulphur dioxide per million, but not, of course, in National Mark preserves. A qualitative test may be made with a simple apparatus devised by Parkes (see illustration: *Analyst*, 1926, 620) consisting of a conical flask fitted with a rubber cork holding a bent two-bulbed thistle funnel which contains a solution of iodine and barium chloride.

The sample, whether jam or other material, is placed in the flask with water, a little porous pot, a few drops of copper acetate solution to retain any sulphide, pieces of marble to replace the air in the flask by carbon dioxide, and finally, just before the cork is inserted, a sufficient quantity of strong hydrochloric acid. When the air is displaced the mixture is gradually brought to the boil, and if the sample contains sulphur dioxide the first few drops of distillate condensing in the funnel produce turbidity due to the formation of barium sulphate, the iodine solution being more or less decolourised if much sulphur dioxide is evolved.

If the presence of any sulphur dioxide is indicated a quantitative determination must be made. A larger amount of sample is distilled with the same reagents and the distillate collected in a receiving flask containing excess of an iodine solution of approximately decinormal strength. During the greater part

of the distillation the condenser tube should dip below the surface of the iodine solution.

When the operation is completed the sulphuric acid formed in the distillate is determined as usual by precipitation with barium chloride, and the sulphur dioxide in the sample calculated from the weight of barium sulphate obtained.

Salicylic and Benzoic Acids may be separated from the sample by shaking an aqueous extract acidified with sulphuric acid with ether, which is washed with a little water, divided into two portions and evaporated in porcelain dishes. The residue in one is tested with weak ferric chloride for the violet colour given by salicylic acid. The slight colour extracted from the jam is usually not enough to interfere with the qualitative test. In a quantitative determination by colorimetric means the jam extract is first treated with a clarifying agent to remove the colour.

The residue in the second dish is examined for crystals of benzoic acid; about 1 ml. of concentrated sulphuric acid and a small crystal of potassium nitrate are added and the dish heated on a boiling water-bath for half an hour. The contents, which should be nearly colourless (slightly yellow if much benzoic acid is present) are diluted with a little water and cautiously made alkaline with ammonia, boiled to decompose any nitrite, cooled and treated with a fresh colourless solution of ammonium sulphide. If benzoic acid is present a red-brown ring or coloured solution of the ammonium salt of meta-diaminobenzoic acid is formed.

Minute traces of salicylic acids may be derived from the fruit composing the jam.

Similarly when the turmeric test for boric acid is applied to the ash of fruit a slight reaction is frequently obtained owing to the presence of a trace occurring naturally.

Tartaric Acid. Regulations made under the Agricultural Produce (Grading and Marking) Act, 1928, require "Select Cider, Champagne process" to be free from any acid foreign to apples, and "Select" cider to contain not more than 1 g. per litre of tartaric or citric acids. The absence of tartaric acid can be shown qualitatively; 3 mg. of tartaric acid by the test described gives a distinct precipitate of calcium racemate.—J. King, *Analyst*, 1933, 135.

The method is applicable to food substances such as jellies, jams or other fruit products, but these may require preliminary treatment for the removal of colloidal matter, etc.

Canned Fruits

Statutory Rules and Orders (1933, No. 538) made by the Minister of Agriculture and Fisheries prescribe grade designations and grade designation marks for apples, blackberries, cherries, and certain other fruits, produced and canned in England and Wales.

VINEGAR

Vinegar has been described in an old work as that form of acetic acid which is generally preferred for culinary purposes, and which is made by the fermentation of vegetable substances.

This definition recognises the important fact that a true vinegar is produced by a fermentation process, and although the term "vegetable substances" seems rather vague and comprehensive at first, vinegar is actually produced from fermentable matter derived from several sources, and hence we have various descriptive terms such as malt vinegar, wine vinegar, cider vinegar, etc.

When wine, beer and weak spirituous liquids are exposed to the air they become sour owing to the action of a ferment, *Mycoderma aceti*, which brings about oxidation of the alcohol with the production of acetic acid. Various other compounds, including aldehyde, acetic ether, etc., are produced in small quantities at the same time.

Strong wines and spirits are not affected, as the ferment is either killed or its action inhibited. On the other hand, weak

solutions of a pure alcohol do not contain the nitrogenous and other food material required by the organism.

Malt vinegar, sometimes known as British vinegar, is made by brewing a "wort" from malt, i.e., the malt, or mixture of malt and unmalted grain, is crushed and steeped in water at about 60° until by the action of diastase the starch is decomposed with the production of maltose, etc. The process is known as "mashing," and the object is to produce as much fermentable sugar as possible. The cleared extract or wort is treated with yeast to bring about alcoholic fermentation, and the alcoholic "wash" is then transferred to an acetifier, where it is caused to trickle over birch twigs or beech shavings which are impregnated with vinegar to introduce the ferment, meeting with an upward current of air which supplies the necessary oxygen.

A little alcohol is left unconverted to allow for the formation of esters which, with the traces of aldehyde, etc., give the vinegar its characteristic flavour and smell.

The Local Government Board in 1911 described vinegar as a liquid derived wholly from alcoholic and acetous fermentation. A malt vinegar is derived wholly from malted barley or wholly from cereals, the starch of which has been saccharified by the diastase of malt.

This admits of the use of grains other than barley, such as rice and maize, and introduces variations in the composition of vinegars, all entitled to be termed malt vinegar.

Hamill in his Report to the L.G.B. in 1908 refers to the use of acid hydrolysis of maize and rice in preparing a wort, and to the addition of sugars.

Artificial vinegar is any vinegar, or substitute for vinegar, containing, or derived from, any preparation containing any added acetic acid which is not wholly the product of alcoholic and subsequent acetous fermentation.

Vinegar (including all varieties) should contain not less than 4 g. of acetic acid per 100 ml.; arsenic should not exceed 0.0143 g. per 100 ml., and it should not contain any sulphuric or other mineral acid, lead or copper, or any foreign substance or colouring matter except caramel.

With reference to the definition of artificial vinegar, it is pointed out by Cox (*Chemical Analysis of Foods*, p. 201) that the presence of a minute quantity of mercury is strongly indicative of the use of strong acetic acid to fortify a weak vinegar, much acetic acid being now prepared synthetically from acetylene, using a mercury catalyst. In view of the minute quantity present in such a case, ordinary chemical tests will be useless and recourse must be had to electrolysis with the use of a small gold cathode. If the mercury present is not sufficient to produce a silvering effect on the cathode, it may still be detected by the production of a sublimate of red mercuric iodide. With practice and care 0.02 mg. may be detected. The spectroscope affords an even more sensitive test.

DEFINITIONS OF VINEGAR AND MALT VINEGAR

The following definitions are suggested standards for vinegar and malt vinegar agreed between the Society of Public Analysts and other Analytical Chemists and the Malt Vinegar Brewers' Federation:—

- (i) Vinegar is a product of the alcoholic and acetous fermentation of a saccharine solution without any intermediate distillation, except in the case of spirit vinegar as defined in (iv).
- (ii) Malt vinegar should be derived, without intermediate distillation, wholly from malted barley, with or without the addition of entire cereal grain, malted or otherwise, the starch of which has been saccharified by the diastase of malt.
- (iii) When vinegar is demanded, a purchaser should be supplied with malt vinegar, unless due notification is given to the purchaser of the article supplied.
- (iv) The name "Vinegar" may be applied to other products which comply with the definition of vinegar (No. (i) above), provided a prefix is used to denote the origin of the product; thus, "Distilled Vinegar," "Spirit Vinegar."

Distilled vinegar is the product of the distillation of vinegar as defined in No. (i) above, and its source should be denoted; such as, distilled malt vinegar.

Spirit vinegar is the product of the acetous fermentation of a distilled alcoholic fluid.

- (v) "Imitation" or "Artificial" vinegar should in every case be sold specifically marked "Imitation" or "Artificial" vinegar. It is any substitute for vinegar containing acetic acid which is not wholly the product of alcoholic and subsequent acetous fermentation, and shall not contain any acid other than acetic acid.
- (vi) All vinegars and imitation artificial vinegars shall contain not less than 4% *w/v* of acetic acid. They shall not contain any acid other than acetic acid or those acids produced by normal fermentative processes.
- (vii) Caramel may be used as a colouring matter in all vinegar and in "Imitation" or "Artificial" Vinegars.

Wine vinegar is prepared on the Continent by acetous fermentation of inferior wines, the best being made from white wine in France, chiefly at Orleans.

Cider vinegar is principally an American product. It contains a considerable amount of malic acid.

Concentrated vinegar or **vinegar essence** is usually prepared by adding acetic acid to brewed vinegar until 25% to 30% of acetic acid is present (Hamill).

It seems probable that some of these concentrated preparations contain no brewed vinegar, but consist of acetic acid and caramel suitably flavoured. When diluted, they produce a cheap artificial vinegar. In fact, they serve in poor districts for the extemporaneous preparation of vinegar by the retailer, who is frequently too liberal with the water, and so supplies a vinegar containing less than 4% of acetic acid. In a particular instance, 1 gallon of the strong essence, when diluted, yields 12 gallons of the artificial vinegar. Such products are sometimes known by the term "**wood vinegar**."

The Food and Drug Administration of the U.S. Dept. of Agriculture define vinegar, cider vinegar, or apple vinegar, as the product made by the alcoholic and subsequent acetous fermentations of the juice of apples. **Wine vinegar**, grape vinegar: from the juice of grapes. **Malt vinegar** from an infusion of barley malt or cereals whose starch has been converted by malt. **Sugar vinegar** from sugar syrup, molasses, or refiners' syrup. **Glucose vinegar** from a solution of glucose is dextrorotatory. **Spirit vinegar, distilled vinegar, grain vinegar**, from acetous fermentation of dilute distilled alcohol. All vinegars contain in 100 ml. (20°) not less than 4 g. of acetic acid.—*S.R.A., F.D. No. 2, Rev. 4, Aug. 1933.*

Analysis of Vinegar

A general analysis of vinegar will include a determination of the specific gravity, about 1.019 in the case of a good malt vinegar, usually much less, but variable in artificial vinegar; the total solids, in malt vinegar about 2 to 2.5%, may be only 0.2% or 0.3% in artificial vinegar, the ash having figures correspondingly small and giving practically no reaction for phosphates which, of course, are present in malt vinegar.

The ash of vinegar should be tested for reaction and should be alkaline litmus.

The acidity may be determined by titration with N/2 sodium hydroxide solution using phenolphthalein as indicator. 5 or 10 ml. of vinegar are well diluted with water in a large porcelain dish. The colour change is seen more clearly in the white dish, and the end-point may be made still clearer by using a second dish with the same amounts of vinegar and water for comparison. Each millilitre of N/2 NaOH is equivalent to 0.03 g. of acetic acid.

Further analysis should include determinations of **nitrogen** and **phosphoric acid**, and tests for free sulphuric acid, ferrocyanides, arsenic and other poisonous metals.

Ferrocyanides are sometimes used to clarify vinegar. They may be tested for with a weak solution of ferric chloride.

Tests should also be made for sulphur dioxide (see page 446) and other preservatives.

Free mineral acid is improbable if the ash is alkaline to litmus. A further test applied to a little of the vinegar is based on the fact that, in the presence of alcohol, acetic acid in all concentrations gives a yellow colour with methyl orange, whereas a strong acid gives a pink in all concentrations down to 0.005 (Prideaux).

The presence of a small amount of sulphuric acid was at one time permitted.

Free sulphuric acid may be detected and estimated by Hehner's method. Evaporate 50 ml. of sample in a platinum dish with 25 ml. of N/10 NaOH, and ignite at a low temperature. Add 25 ml. of N/10 acid, boil, filter and wash with hot water. Titrate the filtrate and washings with N/10 NaOH using phenolphthalein as indicator. Each millilitre of N/10 NaOH required is equivalent to 0.0049 g. of H_2SO_4 .

The *A.O.A.C.* give the following tentative method for determining free mineral acid (*Methods of Analysis*, 3rd Edn., p. 362).

To a measured quantity of sample add a measured excess of standard alkali, evaporate to dryness, incinerate, and titrate the ash with standard acid, using methyl orange as indicator. The difference between the number of millilitres of alkali first added, and the number of millilitres of acid needed to titrate the ash represents the free mineral acid present.

Pickles and Sauces, made from fruit or vegetables, are permitted to contain benzoic acid to the extent of 250 parts per million.

The benzoic acid may be determined by the method used for Ketchup (*Methods of Analysis (A.O.A.C.)*, p. 337). A weighed quantity is saturated with sodium chloride, made slightly alkaline with 10% soda and made up to volume with salt solution, shaken frequently during 2 hours, squeezed through muslin and filtered. A portion of the filtrate is acidified with HCl, extracted with chloroform four times, the combined chloroform extracts evaporated in a current of dry air, and dried in a desiccator over sulphuric acid until no odour of acetic acid is detected; the residue is dissolved in neutral alcohol and titrated with N/20 NaOH using phenolphthalein.

An alternative method due to Monier-Williams (Report to Ministry of Health, 1927), consists in saturating the sample with sodium chloride, acidifying with phosphoric acid, and distilling in steam into a dish containing N/1 alkali. The alkaline distillate is evaporated, purified by treatment with permanganate, saturated with NaCl, and extracted with equal volumes of ether and light petroleum (b.p. 30° to 50°). The solvent is evaporated in a test-tube and the benzoic acid mixed with sand and sublimed into the upper part of the tube, which is cut off, dried in a desiccator, weighed, the benzoic acid removed, and the tube re-weighed.

BREAD AND FLOUR

Civilised man, living a normal life, derives a large portion of his carbohydrate intake from cereal foods. The Anglo-Saxon, the Latin and the Teutonic races have chosen wheat flour or meal as their main cereal food. A portion of the Teutonic races and of the Eastern peoples uses a considerable quantity of rye flour.

Dr. J. M. Hamill's Food Report No. 14, 1911, to the L.G.B., enumerated milling products in common use as follows:—

“**Wholemeal**” or “**Graham Flour**” (actually whole grain flour).

“**Entire Wheat Flour**” or “**Fine Meal**”—a product obtained by removing a portion of the bran and grinding the rest of the grain. (This includes so-called “Standard” flour.)

“**Households**”—The commercially lower grade of flour obtained from roller mills—it is darkish in colour.

“**Patent Grade**.” Commercially the higher grade flour produced by roller mills. It is a better colour than any other flour produced in the mill.

“**Straight run**” or “**straight grade**”—intermediate in appearance and quality between households and patent grades.

Special flours, prepared from any of the above usually with the object of improving nutritive qualities.

The following special distinctions have recently been applied to stone-ground flour:

(1) “**Stone-milled**” flour refers to any flour produced by stone-grinding.

(2) **Wholemeal** flour contains all the constituents of the original grain, including bran and germ.

(3) **Millstone**-flour contains all the constituents of the grain, *except* the bran. It includes 87% to 90% of the germ. It keeps well under proper conditions.—C. E. Shelly, *Brit. med. J.*, i/1924, 1883; ii/1924, 720.

Bread, flour, meal, millable wheat and wheat offals are defined in Section 20 of the Wheat Act, 1932.

The carbohydrates of six different breads were found to be equally well absorbed and utilised. (White, mischbrot (65% to 72%), Graham (unbolted), whole wheat, “Walliser” and Kinderzweiback (rusks)).—I. Abelin and A. Biderbost, *Biochem. Z.*, 1932, 247, 429.

With regard to the question of the best type of flour and bread made from it, Dr. Hamill, in the above report, says:—

The great practical difficulty in endeavouring to define any one variety of flour in terms of protein content, mineral content, or other criteria, is that such a definition to be effective would require preliminary standardisation of wheat, which is impracticable in view of the fact that wheat supplies vary from different parts of the world. It is evident that, unless we live wholly on bread, which is not desirable, the differences between one bread and another do not matter much.

With regard to choice of bread for children, however (though here also a varied diet is insisted on) it is stated—“For those children who live largely on bread—there appears to be advantage in bread from flour of the “*entire*,” wheat class or from wholemeal in which the bran is very finely ground. In these the presence of the so-called offal, including the germ, secures a somewhat larger quantity of mineral matter and of suitably combined phosphorus or other substances as yet unknown, which has been proved to be of importance.

The above view is illustrated and supported by taking one factor alone—the albuminoid content. The albuminoids in a variety of wheats—Argentine, Australian, English, Canadian, Indian, etc.—may range from 8% to 16% of the grain.

Grain arrives in this country from various parts of the world at divers times of the year, according to the respective local seasons, and the miller's labours are taxed to blend these wheats of varying qualities to produce a grist which when milled will provide a flour suited to modern baking methods.

The controversy as to the respective merits of wholemeal and white bread has produced a constant stream of literature for a generation and the battle of opinions still continues. The **Standard Bread** agitation started in 1911. Standardisation of flour, as originally understood, is impossible, but its control is as important as, if not more important than, the standardisation of drugs, and the quality of flour (and other foodstuffs) should be kept at the highest possible level.

"Standard" bread was defined as bread made from unadulterated wheat flour containing at least 80% of the whole wheat including germ and bran.

Spring wheat, grown mainly in the North-Western States and in Canada, is usually harder and slightly richer in protein than the winter wheat, which is somewhat more starchy. In general, a rather hard wheat of more than average protein content is preferred for the manufacture of bread flour, but the wheats with most protein do not necessarily make the best flour.—*Food Products* (1924), H. C. Sherman.

The nitrogen content of wheat was found to be increased only by the heaviest nitrogenous manuring. This increase did not necessarily improve the baking quality.—E. A. Fisher and C. R. Jones, *J. agric. Sci.*, 1931, 21, 574.

The word "**Semolina**" is given to varied products according to the fancy of the miller. The dictionary application of the name is "coarsely ground and carefully purified milling products, especially hard wheat used for macaroni and in cookery." Others apply it simply to a "physical condition" of flour. Others, again, definitely hold that the semolina obtainable commercially is the hardest portion of the endosperm of the wheat grain, and is obtained in a granular form by adjusting the rollers sufficiently far apart, so as not to crush the granules.

The germ differs considerably in composition from other parts of the grain. Placed side by side (from W. Jago—transposed from his figures into percentages) the amounts of certain constituents of (a) a **wheat mixture**, (b) one of the **semolina** products—that coming from the second and third "breaks," (c) "**flattened germ**" from the same mixture and (d) **bran** are as follows :

	Wheat	Semolina	Flattened germ	Finished bran
<i>Moisture</i>	38·171	43·041	14·822	22·598
<i>Soluble extract</i> . .	16·403	13·577	43·940	17·567
<i>Soluble protein</i> . .	4·361	3·191	15·652	2·259
<i>Crude gluten (dry)</i>	19·093	19·416	—	—
<i>Ash</i>	4·835	3·394	5·501	12·742
<i>Phosphoric acid</i> . .	2·465	0·747	3·207	7·322
<i>Fat</i>	4·993	4·311	11·982	3·068
<i>Cellulose</i>	9·671	12·627	4·776	34·4

Flour contains 0·12% of glucose and fructose, 0·25% of sucrose, and 0·25% of lævulosides. Wheat bran contains 0·10% of glucose and fructose and 5·0% of sucrose and lævulosides. Wheat germ contains 12% of sucrose and lævulosides.—R. Geoffroy, *Bull. Soc. chim. Fr.*, 1932, 1491.

The proteins of rye bread were found to be superior to those of wheat bread. Soya proteins seemed to supplement rye bread flour.—S. K. Kon and Z. Markuze, *Biochem. J.*, 1931, 1476.

Mineral constituents in the ash of wheat and other cereals:—Lime, it has been stated, ranges from 1% to 10%; magnesium oxide gives an average of 12·11%; silica rarely reaches 5%, being usually less than 2%; P_2O_5 constitutes an average of 49% to 50%; Iron, as Fe_2O_3 , averages 1·1%.

Figures giving flour analyses vary greatly (*cf.* Atwater and Benedict, Hutchison, Tankard, etc.).

Iodine in wheat products. Bran contains 3·8, germ 3·0, and wholemeal 2·5 parts per million. White flour contains less than 1 in 5,000,000.—*Brit. med. J.*, i/1925, 764.

White flour and bread are robbed by the miller of iodine, along with valuable salts and vitamin B.—Review of Swale Vincent's book on internal secretions and the ductless glands.—*Brit. med. J.*, i/1925, 369.

Whole wheat and oatmeal are effective in regenerating the hæmoglobin of rats suffering from nutritional anæmia in proportion to the iron content of the supplement. White flour was not effective in proportion to its iron content, nor was it made as effective as whole wheat by the addition of iron or copper or both of these. Thus whole wheat seems to contain some factor, lacking in the flour, which can supplement the inorganic iron and copper.—M. S. Rose and E. M. Vahlteich, *J. biol. Chem.*, 1932, 96, 595.

Nature, of May 4th, 1911, had a good article on the position on this and allied matters.

Although the difference in protein between roller-milled flour and stone-ground flour is not great, it is the quality not the quantity of protein that matters, and the proteins of the germ are particularly suited for promotion of growth. In the case of children who have abundant mixed diet this special protein is obtained from other sources, but where the diet is mainly composed of bread the difference might be of considerable importance.—R. Hutchison, *Brit. med. J.*, ii/1924, 720.

With regard to the **phosphorus** in wheat bran,—this was first thought to be inorganic—then to be connected with the nuclein or salts of nucleic acid—but researches show that only 33% of the phosphorus could be accounted for in this way, and that the chief phosphorus compound is a magnesium-calcium-potassium salt of a phospho-organic acid,—probably identical with anhydro-oxy-methylene-diphosphoric acid,—an acid which is widely distributed in the vegetable kingdom.—*Brit. med. J.*, ii/1911, 861, 1137.

The higher animals are apparently not endowed with the power of preparing their own organic phosphorus compounds from inorganic phosphorus, nor indeed, are they probably able to form such compounds of one group from those of another. These bodies are of far-reaching importance to the bioplasm.

A healthy man accustomed to a full mixed diet requires for maintenance of phosphorus equilibrium about 1·5 g. of phosphorus, or nearly 3·5 g. of phosphoric acid per diem; the organic combination seems to be best. The calcium requirement is equivalent to about 0·7 g. of calcium oxide per diem.—*Nature*, ii/1910, 148.

Vitamin B Content of White Bread and Flour. Rat experiments showed that mothers fed with extract made from wholemeal flour did better than those fed on extract from white flour, i.e., there is more vitamin B in wholemeal than in white flour. The author concludes that white bread contains sufficient vitamin B to supply the needs of a rat both for growth and reproduction. White flour contains a little vitamin B, but the main source is the yeast.—Gladys A. Hartwell, *Biochem. J.*, 1924, 120.

Whilst the addition of yeast has no material effect on its "B" content the addition of wheat germ produces a bread rich in vitamin B, and yet distinct from wholemeal bread which contains bran—an indigestible substance.—W. Cramer and J. C. Mottram, *Lancet*, ii/1927, 1090, see also *ibid.*, 1153.

Bulk for bulk, white bread has more calories available for nutrition than brown bread. Vitamin B is present in the yeast introduced into the white bread, and if the effect of the "roughage" is to produce instead of a formed stool one of more fluid consistency it is doubtful whether it confers any known benefit on a healthy person.—Sir T. Horder, *Lancet*, ii/1927, 103; see also *ibid.*, 201.

Yeast may be dispensed with, and actually much bread on the market to-day has been aerated by incorporating already-formed carbon dioxide with the dough. If persulphate of potash be used as an improver, ammonium persulphate may be formed by the gluten, and this, acting as a reducing agent, is likely to destroy any vitamin introduced by the yeast.—J. Oliver, *Lancet*, ii/1927, 254.

Unable to keep rats alive longer than 5 weeks on a B-deficient diet, whereas the addition of wheat germ 2% enabled them to live normally.—M. J. Rowlands, *Lancet*, ii/1927, 305.

It has been shown that the highest proportion of yeast (fresh) normally employed in bread-making will not supply white bread with more than 1/7th the amount of vitamin B found in good, wholemeal bread and it has been proposed to solve the problem by replacing white by wholemeal bread. Such a replacement, however, would create serious milling difficulties and would involve extensive alteration, or even scrapping, of much expensive milling plant, with a consequent rise in the cost of the bread. A practical alternative is the **addition of dried yeast** to ordinary white flour. Dried yeast is several times more potent in vitamin B than the fresh yeast employed in bread-making, and if used in a proportion of 2% to 4% would yield a palatable bread containing as much vitamin B as the finest wholemeal product.—S. G. Willimott and F. Wokes, *Lancet*, ii/1928, 673.

L. Hill and M. Flack stated: "**Wheat germ alone added to white flour** makes this an adequate food on which animals can live healthily. This proves that the lack of cellulose has nothing to do with the insufficiency of white flour, and that whatever the active principle may be, it is present *no less in germ than in bran and sharps*. In fact, rats did better on white flour plus germ than on white flour plus sharps, bran, and a trace of germ."

White wheat flour, plus fresh meat, plus cod-liver oil was found to be insufficient to promote growth in pigs for more than about 7 weeks. The addition of 2 oz. per pig of dried brewers' yeast made the diet satisfactory. 0·5 pint to 2·0 pints of stout per pig daily had a similar but less marked effect.—A. H. Blisset and J. Golding, *Biochem. J.*, 1931, 349.

Flours milled from dry land wheat contained more carotene than those milled from irrigated land wheat.—A. G. O. Whiteside, *Bull. Dep. Agric. Can.*, No. 154, 1931.

Wheat meal in all-mash rations.—L. W. Rhys, *Harper Adams Util. Poult. J.*, 1932, 352.

National Mark Flour is in *Three Grades*

ALL-ENGLISH (Plain).—A general purpose flour, but mainly for biscuit-making.

ALL-ENGLISH (Self-raising).—Household flour for pastries, puddings, etc.

ALL-ENGLISH (Yeoman). A bread-making flour made of Yeoman wheat, the variety created at Cambridge by Sir Rowland Biffen to produce a loaf equal to that made of best Manitoban wheats.

★**Vita** (T.M.478,917) **Wheat** is thoroughly cooked. The bran is subjected to a preliminary cooking before the final baking.—*Brit. med. J.*, ii/1927, 21.

★**Energen** (T.M.337,793) **Bread**, according to the makers, is prepared without yeast, drugs or chemicals, and contains but one-fifth of the moisture usually present. Over 40% of the wholemeal bread consists of whole wheat grain.

Bleaching of Flour

Bread is sold legally by weight, and too often the baker slack-bakes his loaf and leaves as much water in it as possible (it should not exceed 15%—Kenwood); in consequence it is less digestible, more dough-like, and less nourishing.

In a Local Government Board Report (Food Report No. 12, 1911) Drs. J. M. Hamill and G. W. Monier-Williams, dealing with the action of **nitrogen peroxide** (N_2O_4), indicate that the colour of the bleached flour may change again, i.e., become yellow or still more bleached according to circumstances. The quantity of nitrous acid or nitrites formed is proportional to the N_2O_4 used. The N_2O_4 is present in the flour as **nitric** and **nitrous acids** or **nitrates** and **nitrites**. In highly bleached flour (1 kilo with 300 ml. of N_2O_4) an increase in the amounts of soluble proteins and soluble carbohydrates takes place. The amount of soluble nitrogen is doubled (due entirely to the solubility of gliadin in HNO_3 of certain strengths). About 6% to 7% of the nitrogen

introduced as N_2O_4 is absorbed by the fat of the flour—it undergoes change as does an oil on oxidation. The rate of digestion was greatly retarded if the starch had been previously treated with N_2O_4 . *Bleaching exercised an inhibitory effect on the salivary digestion of flour.*

It is stated (*J. Soc. chem. Ind., Lond., 1912, 40*) that nitrites *do not interfere with the action of diastase on starch*, also that *pancreatic digestion is not inhibited by relatively large quantities of nitrites*. Further, that direct experiments with the compound of the colouring matter of the flour with oxides of nitrogen showed that this is not poisonous nor does it have any perceptible action on the blood.

The bleaching of flour causes physical and chemical changes in the ether-soluble part and in the gluten content of white flour, as well as destruction of diastase and vitamins.—F. Bordas, *Ann. Hyg. publ., Paris, 1931, 9, 65*.

The proportion of benzoyl-peroxide used to bleach a flour may be determined by converting the unchanged peroxide into benzoic acid by means of sodium hydroxide in the presence of acetone. The total benzoic acid is oxidised to salicylic acid and measured by matching the colour obtained with 1 drop of ferric chloride solution with the colour of control solutions containing salicylic acid.—J. R. Nicolls, *Analyst, 1933, 4*.

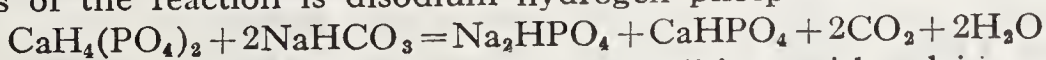
Calcium Sulphate in Baking Powder and Self-raising Flour

Baking powders in use, according to a L.G.B. Report on "The Presence of Calcium Sulphate in Baking Powder and Self-raising Flour" (Food Report No. 13, 1911, by Dr. Hamill), may be classed into two groups (1)—this being by far the larger—tartaric powders in which the acidic constituent is tartaric acid, cream of tartar, or a mixture of these, and (2) the phosphate powders, the acidic constituent of which is calcium acid phosphate, together with sodium bicarbonate in all cases. Ammonium carbonate is extensively ingested *per os* as it is a necessary ingredient in the baking of sponge cakes and other light bread products. Alum is not now employed, although it is capable of acting as an acidic constituent, and was formerly much used. In an addendum by C. H. Cribb, regarding the use of phosphate baking powders and the alleged utility of calcium sulphate in them, it is stated:

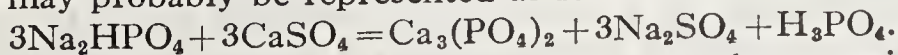
When calcium sulphate is mixed with sodium bicarbonate in the presence of water, carbon dioxide gas is evolved according to the following equation:—



The evolution of gas commences immediately, but is very slow, so that at the end of half an hour 59%, and after 1 hour 79%, of the theoretical quantity was found to have been liberated, and even after 3 hours the reaction was not complete. When calcium acid phosphate acts upon sodium bicarbonate one of the products of the reaction is disodium hydrogen phosphate thus:—



and this salt in turn reacts under suitable conditions with calcium sulphate, giving rise to phosphoric acid, which in turn can liberate a fresh quantity of carbon dioxide from any carbonate which may be present. The first part of the reaction may probably be represented as follows:—



In actual baking experiments with a baking powder containing calcium sulphate, 75% of the calcium sulphate was recovered unchanged from the finished loaf. Other experiments would seem to indicate that the calcium sulphate which has disappeared as such in the loaf is again re-formed by the agency of the acid in the gastric juice when the bread is eaten.

Calcium sulphate occurs in commercial calcium acid phosphates to the extent of 2% or 3% up to 50%. The proportion varies according to the method of preparing the calcium phosphate.

It is generally made from bone ash by means of phosphoric and sulphuric acids. When commercial phosphoric acid alone is added to the bone ash, a product can be obtained containing as little as 2% or as much as 9% of calcium sulphate. When sulphuric acid alone is used, the product may contain as much as 50% of calcium sulphate; mixtures of these acids give values intermediate between the extremes mentioned. Calcium sulphate is sometimes deliberately added as a diluent. To keep the acid phosphate and sodium bicarbonate from

too intimate contact, a neutral non-hygroscopic powder, known as "filling," is added, such as corn flour or more usually rice flour. The filling may be 50% or more of the baking powder.

The following recipes are given in the report:—

Calcium acid phosphate	50	37	2	77
Sodium bicarbonate	25	23	1	41
Maize starch, rice flour or ground rice	25	40	3 to 10	50 to 100

From $\frac{1}{2}$ oz. to 1 oz. of the powder is used for each pound of flour, hence if the calcium acid phosphate of the first powder contained 50% of calcium sulphate $\frac{1}{2}$ oz. of the powder would contribute over 50 grains of calcium sulphate to the flour. The same remarks apply in regard to the calcium sulphate introduced with the phosphate, 70 grains per lb. being contained in the above flour if the first ingredient is 50% phosphate. The phosphate baking powders do not keep well and are not found in retail trade. Bakers mix the ingredients when required.

Self-raising flours are made thus:—

Calcium acid phosphate	6 lb.
Sodium bicarbonate	3 lb.
Flour	280 lb.

Dr. Hamill made the following recommendations (*inter alia*):

(a) *Manufacturers of acid phosphates* should not prepare even their cheapest qualities of acid phosphate for sale as food ingredient, in such a way that they contain more than 10% of calcium sulphate.

(b) *Bakers, self-raising flour makers*, and others using acid phosphate in the preparation of food, should limit themselves to acid phosphate of high commercial quality—calcium sulphate not to exceed 10%.—L.G.B. Report and Editorial comment, *Chem. & Drugg.*, i/1911, Index Fol. 545.

The Food and Drug Administration of the U.S. Dept. of Agriculture define baking powder as the leavening agent produced by mixing an acid-reacting material and sodium bicarbonate with or without starch or flour. Yields not less than 12% available carbon dioxide. The acid-reacting materials are: (1) Tartaric acid or its acid salts, (2) acid salts of phosphoric acid, (3) compounds of aluminium, (4) any combination in substantial proportions of the foregoing.—*S.R.A., F.D., No. 2, Rev. 4, Aug., 1933.*

Improvers

Sodium chloride has long been used, the usual amount being $3\frac{1}{2}$ lb. per sack of flour.

Gelatinised potato, or, as it is called "**fruit**," has been used to assist the yeast plant in its function of vesiculating and maturing the dough with the least trouble to the baker.

Sour flour also materially improves baking qualities, when added in the proportion of 5 to 275 of fresh-milled flour.

Acid salts (persulphates and acid phosphates). The yeast plant develops best in a medium possessing definite acidity, and there must be available in the dough a supply of nitrogenous food and of the phosphatic sugar complex. The addition of acid enables the British miller to compete with overseas competitors. Previously it is stated, overseas flour was improved in transit, both in colour and acidity, making it more desirable from the user's point of view for baking without yeast.

With regard to flour for yeast panification, here also acidification is desirable. It was found that a flour, for example—to give an extreme case—containing 12.71% of albuminoids and a wet gluten figure of 39.4, gave a loaf badly aerated and with a crumb like indiarubber. The addition of $\frac{1}{2}$ oz. of ammonium persulphate per 280 lb. of flour changed the character of the flour and gave

a good loaf. On the other hand, a flour with 8·2% of albuminoids—and correspondingly more carbohydrate—and 24·67% of wet gluten gave an excellent loaf.

Ammonium acid phosphate to the extent of, say, 4 oz. per sack, it is claimed, will provide a nitrogenous food for the yeast and will provide the necessary acidity. It may be used in conjunction with calcium acid phosphate.

Persulphates are stated to act like ammonium acid phosphate as stimulants in a dough made of flour, yeast, salt and water.

Chlorine. The use of this is said to be beneficial, in rendering flour amenable to maturation by yeast.

Suggested maximum quantities are:—

Calcium acid phosphate	0·3 % = 13½ oz. to 280 lbs.
Ammonium acid phosphate	0·2 % = 9 oz. to 280 lbs.
Persulphates	0·04% = 1·8 oz. to 280 lbs.
Chlorine	0·07% = 3 oz. to 280 lbs.
Nitrogen peroxide	8 parts of nitrites per million.

A mixture of about equal proportions of acid potassium and magnesium phosphates and flour is said to be an effective “improver.”—Kenwood.

Treatment of flour is also carried out in Germany, Holland and other countries. In favour of persulphates.—W. Jago, *Lancet*, ii/1926, 1038.

Persulphates and other chemicals are foreign additions to flour, and constitute, when added to flour, substances which render this food *not of the nature of flour*.—A. R. Tankard, *Lancet*, ii/1926, 1243.

“**Baker’s eczema**” due to use of flour containing potassium persulphate to the extent of 6·3 parts per 100,000.—A. R. Tankard, *Lancet*, ii/1923, 279.

There should be no difficulty in tracing the use of improvers, the commonest being potassium persulphate.—J. T. A. Walker, *Lancet*, i/1925, 1163; See also *ibid.*, 1273.

“**Baker’s Itch.**” Immunity of French and American bakers to this is attributed to the fact that the use of “improvers” is illegal in those countries. One of the commonest “improvers” to which the complaint may be traced is potassium persulphate, which decomposes on addition of water with liberation of oxygen and formation of potassium acid sulphate, the reaction being expressed thus: $2K_2S_2O_8 + 2H_2O = 4KHSO_4 + O_2$. “Baker’s itch” was unknown in this country before introduction of “improvers.”—J. T. Ainslie Walker, *Lancet*, i/1925, 1163.

Improvers and Dermatitis. Dr. Parsons on behalf of the Ministry of Health made investigation on the subject in the early part of 1922. One of his conclusions was that probably 50% of cases could not be true “baker’s itch” acquired as result of baking. During the war and the period of demobilisation the term was widely used as a euphemism for scabies and heterogeneous skin lesions. Medical opinion was that no increased prevalence of the true complaint was found. Contact with *sugars* and not foreign flour or bleaching processes accounts for a large proportion. A small percentage of cases found in which after years of immunity a baker may become sensitised to flour protein. 2 cases were found.—*National Bakers’ Ass. Review*, Nov. 9th, 1923.

Analysis of Flours

A few years ago—in 1925 (see Edn. XVIII., Vol. II, p. 112)—the ash-percentage of flours bought in various parts of London was found to be within normal limits—approx. 0·3% to 0·5%. It is generally understood that an ash of 1% would indicate mineral adulteration or low-grade flour.

In the case of self-raising flour, several samples showed about 2% of inorganic residue on ignition.

Detection of Bleaching of Flour.

This can be effected by the production of a red colour with the Griess-Ilosvay reagent, consisting of sulphanilic acid and α -naphthylamine in acetic acid, or by means of the following test (Allen, 5th Edition, Vol. I, 579). The reagent is prepared by dissolving 1 g. of sulphanilic acid in 100 ml. of hot saturated ammonium chloride solution, and then adding 1.5 g. of phenol and 100 ml. of 2 N hydrochloric acid. The sample of flour, 5 g., is macerated with 100 ml. of distilled water, filtered and 50 ml. of the filtrate mixed with 1 ml. of the reagent. After 15 minutes, ammonia (sp. gr. 0.880) is added and the liquid stirred. An orange-red colour is produced with nitrites and is proportional to the amount present. Minute amounts, of the order of 5×10^{-6} g. HNO_2 in 50 ml., give a distinct yellow colour. As a simple test for bleached flour, the shaking of about $\frac{1}{2}$ oz. with 2 oz. of petrol, the liquid taking up a yellow colour unless the sample has been bleached, is well known.

According to Kenwood, *when over 1.5 parts of nitrites per million are present it may be presumed that the flour has been bleached.* The very slight reaction for nitrites given by all the samples examined, including a known pure specimen, is probably due to the fact that, as stated by Allen, unbleached flour frequently absorbs small portions of nitrites from the air, especially in industrial towns. At any rate, it is known that even unbleached flour gives a slight nitrite reaction.

The petrol test does not seem to give conclusive evidence. Thus, although a colourless extract denotes thorough bleaching, there appears to be the possibility that a dark flour might be treated just sufficiently to render it normal in appearance. A very pale petrol extract, with absence of nitrites, may also be indicative of the use of other bleaching agents, such as halogens or ozone.

The data obtained in 1925 indicated that the sale of bleached flour is widespread.

To detect flour bleached by chlorine. The chlorine apparently occurs in or with the extractable fatty matter, being readily soluble in the usual fat solvents. Best extracted by shaking the flour with a mixture of alcohol, ether and light petroleum.—*Analyst*, 1926, 150.

Foreign mineral matter may be shown by shaking the sample with chloroform; the flour floats and the mineral matter separates and may be estimated.

Copper sulphate, probably employed to prevent or destroy fungoid growth in the corn, has been detected in flour and bread.—Kenwood.

Moisture in Flour.—This should not exceed 15%.—Kenwood.

FOOD PRESERVATIVES

The Minister of Health issued Regulations based on recommendations of the Departmental Committee on the Use of Preservatives and Colouring Matter in Food, and providing for the prohibition of the importation and sale of articles of food to which preservatives and other specified substances have been added. These Regulations in general came into operation on January 1st, 1927.

The Regulations prohibit the use in foodstuff and drinks, of preservatives except those mentioned below, and then on condition that they do not contain a larger proportion than is specified, and are properly labelled.

"Preservative" includes any substance which is capable of inhibiting, retarding or arresting the process of fermentation, acidification or other decomposition of food or of masking any of the evidences of putrefaction.

The term does not include Salt, Saltpetre, Sugars, Vinegar, Acetic or Lactic Acid, Alcohol, or potable Spirits, Spices, Herbs, Hop Extract, Essential Oils used for flavouring, Glycerin or any substance added by the process of curing known as smoking.

PERMITTED PRESERVATIVES

Food	Preservative	Parts per million	
(1) Sausage and sausage meat containing raw meat, cereals and condiments	SO ₂	450 =	3.15 grains per lb.
(2) Fruit and fruit pulp not dried:—			
(a) Cherries	SO ₂	3000 =	21.0 " " "
(b) Strawberries and raspberries	SO ₂	2000 =	14.0 " " "
(c) Other fruit	SO ₂	1500 =	10.5 " " "
(3) Dried fruit:—			
(a) Apricots, peaches, nectarines, apples and pears	SO ₂	2000 =	14.0 " " "
(b) Raisins and sultanas	SO ₂	750 =	5.25 " " "
(4) Unfermented grape juice and non-alcoholic wine made from such grape juice if labelled in accordance with the rules contained in the second schedule to these Regulations	Ac. Benz.	2000 =	140.0 grains per gall.
(5) Other non-alcoholic wines, cordials and fruit juices, sweetened or unsweetened	SO ₂ or Ac. Benz.	350 = 600 =	24.5 " " " 42.0 " " "
(6) Jam (including marmalade and fruit jelly prepared in the way in which jam is prepared)	SO ₂	40 =	0.28 " " lb.
(7) Crystallised glacé or cured fruit, including candied peel	SO ₂	100 =	0.7 " " "
(7a) Fruit and fruit pulp not otherwise specified in this schedule	SO ₂	350 =	2.45 " " "
(8) Sugar (including solid glucose) and cane syrups	SO ₂	70 =	0.49 " " "
(8a) Cornflour (maize starch) and other prepared starches	SO ₂	100 =	0.7 " " "
(9) Corn syrup (liquid glucose)	SO ₂	450 =	3.15 " " "
(10) Gelatin	SO ₂	1000 =	7.0 " " "
(11) Beer	SO ₂	70 =	4.9 " " gall.
(12) Cider	SO ₂	200 =	14.0 " " "
(13) Alcoholic wines	SO ₂	450 =	31.5 " " "
(14) Sweetened mineral waters	SO ₂	70 =	4.9 " " "
	or Ac. Benz.	120 =	8.4 " " "
(15) Brewed ginger beer	Ac. Benz.	120 =	8.4 " " "
(16) Coffee extract	Ac. Benz.	450 =	31.5 " " "
(17) Pickles and sauces, made from fruit or vegetables	Ac. Benz.	250 =	1.75 grains per lb.

Sulphur dioxide includes sulphites, and benzoic acid includes benzoates, calculated respectively in terms of sulphur dioxide and benzoic acid.

LABELLING. Special labelling applies to *sausages, sausage meat, coffee extract, pickles and sauces* and (where proportion of benzoic acid exceeds 600 parts per million) *grape juice and wine*. These must bear a label stating the contents are preserved, e.g., "These sausages contain preservative," and in the case of grape juice and wine where it applies "and is not intended for use as a beverage."

The retailer must exhibit a notice in a conspicuous place to the effect that the goods in question contain preservative.

Departmental Committee's Report.

Preservatives may be used to mask unsoundness, or careless methods of production, storage and distribution. A dose of **boric acid**, the most commonly used preservative, is not completely excreted from the system for 5 days, and the tissues are never free—the Committee considered its prohibition justified. **Sodium sulphite**, in amounts employed in foods, has no specific toxic action, but is not harmless, as sulphur dioxide liberated may cause dyspeptic symptoms. The putrefactive odour of decaying meat is removed by treatment with sodium sulphite, and the red, fresh appearance restored. Prof. A. J. Clark, representing the B.M.A., considered that **formaldehyde** and **fluorides** should be prohibited, as they are definitely toxic, as also **borax** preparations, on account of cumulative action, and **salicylic acid** and **salicylates**, on account of powerful physiological action. Preservatives are used in a haphazard way, or even in ignorance, and often no effort is made to do without them. The Committee saw no reason why the sale of cream should not be conducted on the same lines as milk, i.e. without preservatives. They recommended that after two years of grace preservatives in butter and margarine should be prohibited. Addition of preservatives to sausages is undesirable, and should be regarded as a concession to trade necessities, which should eventually be dispensed with. Use of preservatives for packing and dusting of hams is unnecessary. Recommendation that use of preservatives in liquid eggs should be prohibited—freezing an alternative. Preservatives should be unnecessary in alcoholic wines of ordinary strength, but where required sulphur dioxide should be permitted in amounts not exceeding 3 grains per pint. The Committee finally recommended that preservatives be prohibited in all articles of food or drink, offered or exposed for sale, whether manufactured in this country or imported, except with certain exceptions which are given *antea*.

The method of estimating preservatives to be prescribed by the Ministry of Health. Sale of food preservatives should be illegal unless they bear descriptions indicating composition and strength, and are free from impurities, containing not more than 1/100 gr. arsenic or 1/7 gr. lead per lb.—*Brit. med. J.*, ii/1924, 290, 828, 829. See also *Brit. med. J.*, ii/1925, 349; i/1927, 70.

See also *Milk Preservatives*, p. 425 and in addition, *Public Health (Preservatives in Food) Amendment Regns.*, 1926 and 1927, and for earlier information on the matter *E.P. XVIIIth Edn.*, Vol. II, pp. 482, 483.

Earlier References

Formaldehyde irritates the mucous membrane, and prolonged use may cause inflammation of the liver and kidneys. It combines with the proteins of food, rendering them less digestible, and its excretion is slow. The use of formaldehyde should be banned in all cases. (Interim Report of Food Preservative Committee, 1924).—*Nature, Lond.*, ii/1924, 448.

It has been suggested that chemical preservatives may be prejudicial by exerting a selective action on bacteria, restraining the putrefactive types, so that the food appears sound, while allowing more pathogenic bacteria to develop.

A fact of general applicability is that the preservatives are mostly substances foreign to the animal body and are excreted by the kidneys. This organ is particularly sensitive to chemical substances so secreted, and it is therefore a reasonable supposition that their elimination may be locally harmful, particularly to those with defective or damaged kidneys.—*Food Poisoning*, Savage.

Being inimical to the life of putrefactive organisms, preservatives must exercise a retarding effect upon the activity of the enzymes concerned in ordinary digestion, and they facilitate an uncleanly, slovenly treatment of food, rendering it possible to preserve articles in incipient decomposition for some time with an appearance of freshness.

Salicylic acid is depressing, liable to be cumulative in action, and has irritant effect on the kidneys; benzoic acid is irritating; formaldehyde delays gastric digestion, and sulphurous acid is a gastric irritant.

The presence of preservatives in **canned articles** which have been sterilised by heat, indicates that the addition was made, prior to canning, to *check decomposition*. With good materials, their use is unnecessary.—Kenwood.

Liquid egg containing boric acid is refused entry into the U.S.A. for use as a food. In a London suburb a sample of sponge cake was found to contain 35 grains of boric acid per lb., the source of which was egg-yolk shipped from China.—per *Pharm. J.*, i/1923, 487.

Dried Eggs.—Total number of viable bacteria varies, but in general is greater in that dried on vacuum drum than that prepared by the spray process, results varying from 350 to a million per g. of liquid egg in the former case, and from 45,000 to over 2 millions in the latter case. The characteristic smell of doubtful eggs is almost lost in the drying process.—per *Analyst*, 1926, 98.

Preservatives of meat extract and vegetable infusions (senna leaf). Sulphur dioxide 0.3% and several others were found ineffectual. Sodium benzoate (0.25%) preserved in acid solution but fermentation occurred in alkaline and neutral media. Glycerin 45% could not be relied on in acid or neutral media but was effective in alkaline solution. Benzoic acid, salicylic acid, glycerin and alcohol were found to be the best; benzoic better than salicylic acid. Formaldehyde 0.05% preserved in all solutions. It approaches the ideal.—*Chem. & Drugg.*, i/1922, 813.

In America "canning compounds" are sold, and an example is given of one consisting of boric acid 95% and sodium chloride 5%. This had a selective antiseptic action, inhibiting the growth of some varieties of *colon bacilli*, but *B. enteritidis*, *B. paratyphosus*, *B. typhosus* and others grew readily in the concentration of the compound which would be used in canning.—*J. Amer. med. Ass.*, per *Pharm. J.*, i/1923, 431.

A suggestion to retain boric acid as a preservative for meat products, since, unlike sulphur dioxide, it does not remove the taint from unwholesome food. Its deleterious effects are probably greatly exaggerated, since workers in the Saffimes of Tuscany may excrete 8 grains daily, and yet the death rate is less than that of Italy in general.—*Chem. & Drugg.*, i/1925, 196.

Ptomaine poisoning in man is exceedingly rare; the majority of the cases of food poisoning are due to living specific microbes implanted in food or drink, and small quantities of boric acid would neither prevent their access nor kill them if present. Food, such as sausages, containing preservatives, has often been associated with acute gastro-enteritis. Boric acid would keep food "free from taint," but it might mask a far greater danger than mere taint. Greater care needed in the handling of food and the prohibition of preservatives enforces this. It is monstrous to insinuate that the Ministry of Health has done wrong in putting a stop to the doctoring of food by chemicals.—A. Rutherford, *Lancet*, ii/1928, 768.

The following **food preservatives are approved in Germany**:—ethyl and propyl esters of *p*-hydroxybenzoic acid and the sodium salts, hexamine (in fish products, caviare, etc.), hydrogen peroxide (in fish jellies), benzoic acid and sodium benzoate, boric acid (in anchovies, caviare, etc., and egg-yolk for use in fancy bakeries), formic acid (in fruit juices, etc.), and sulphur dioxide.

Other Methods of Food Preservation

Carbon dioxide in a concentration of about 10% doubles the storage life of chilled beef and is also useful for storing bacon, which can be kept in it at 5° for 9 weeks. The absence of oxygen prevents rancidity and the carbon dioxide prevents "taint." Pork has been kept fresh in it for 17 weeks.—Rep. of Food Investigation Board for 1932, *Lancet*, ii/1933, 303.

Freezing. Deterioration of meat is most rapid at -2° to -3° and almost nil at -20° to -25° . The interplay of two factors determines the rate of deterioration at any temperature: removal of water by ice formation, which changes the pH, and fall of temperature, which slows down chemical change.—Rep. of Food Investigation Board for 1932, *Lancet*, ii/1933, 303.

DYES USED IN COLOURING FOODS

The following aniline dyes have been found by various authorities to be harmless for colouring foods. Many were given in a list issued by the National Confectioners' Association of the United States in 1899, and to these have been added other colours, specially indicated, which are permitted by the Governments of Canada, the United States and certain Australian States. The number placed before each colour is that of the COLOUR INDEX OF THE SOCIETY OF DYERS AND COLOURISTS (1924), which is

intended to be the standard reference book of the English-speaking countries.

*The dyes marked with a * are stated in the Colour Index to be actually used for colouring edibles.*

The use of these dyes is not prohibited by the Public Health (Preservatives, etc., in Food) Regulations, 1926-7. These Regulations render the use of the following colouring matters illegal:—

1. Compounds of antimony, arsenic, cadmium, chromium, copper, mercury, lead and zinc.
2. Gamboge.
3. Picric acid (7), *syn.* carbazotic acid; victoria yellow (8), *syn.* saffron substitute and dinitrocresol; manchester yellow (9), *syn.* naphthol yellow and martius yellow; aurantia (12), *syn.* imperial yellow; aurine (724), *syn.* rosolic acid and yellow coralline.

The Canadian regulations forbid the use of aniline dyes containing more than 10 parts per million of arsenic, As_2O_3 , or heavy metals (iron excepted), and the dyes must not be used in quantities exceeding 2 grains per lb. (1 in 3500). The adoption of any colour for pharmaceutical or toilet preparations is governed by the composition of the article, alkalis or acids affecting some of the dyes, whilst the fluorescence of colours, such as eosin, may be objectionable in a medicine but suitable in a toilet preparation. —*Chem. & Drugg.*, 1924, 438.

Blue

- 689 **Gentian Blue 6B**, *syn.* SPIRIT BLUE, ANILINE BLUE.

The hydrochloride, sulphate or acetate of phenylated *p*-rosaniline and rosaniline. Insoluble in water. The acetate is readily soluble in alcohol, the sulphate and hydrochloride sparingly soluble.

- 861 **Coupler's Blue**, *syn.* WATER-SOLUBLE INDULINE.

Sodium salts of sulphonated mixtures of amino-diphenyl-diamino-triphenyl-triamine and tetra-phenyl-tetramino-phenyl-diphenazonium-chloride.

Soluble in alcohol and water.

- 1180 **Indigo Carmine** (Aus., Can., U.S.A.).

Sodium salt of indigotin-5 : 5'-disulphonic acid.

Soluble in water, sparingly soluble in alcohol.

Green

- 670* **Light Green S.F. Yellowish** (Aus., Can., U.S.A.).

Sodium salt of dibenzyl-diethyl-diamino-triphenylcarbinol tri-sulphonic acid anhydride.

Soluble in water, almost insoluble in alcohol.

Picric acid gives no precipitate (distinction from green basic dyes).

Brown

- 331* **Bismark Brown G** (Aus.).

Hydrochloride of benzene-*m*-diazo-bis-*m*-phenylenediamine.

Soluble in water and alcohol.

- 480 **Chrysamine R**.

Sodium salt of ditolyl-diazo-bis-salicylic acid. Water-soluble.

Orange

- 26 **Crocein Orange**.

Sodium salt of benzene-azo- β -naphthol-6-sulphonic acid.

Slightly soluble in water, moderately soluble in alcohol.

- 150* **Tropæoline 000**.

No. 1, or Orange 1 (Aus., Can., U.S.A.) Sodium salt of *p*-sulphobenzene-azo- α -naphthol.

Soluble in water and alcohol.

Red

- 46 **Archil Substitute.**
p-nitrobenzene-azo- α -naphthylamine-4-sulphonic acid.
 Aqueous solution reddish-brown.
- 79* **Ponceau 2R**, *syn.* SCARLET R.
 Sodium salt of *m*-xylene-azo- β -naphthol-3 : 6-disulphonic acid.
 Yellowish-red solution in water, insoluble in alcohol.
- 80* **Ponceau 3R and 4R**, *syn.* CUMIDINE RED (Aus., Can., U.S.A.).
 Sodium salt of cumene-azo- β -naphthol-3 : 6-disulphonic acid.
 Ponceau 3R is made from crude cumidine, and Ponceau 4R from pseudo-cumidine.
 Water—cherry-red solution; slightly soluble in alcohol.
- 88* **Bordeaux B**, *syn.* ACID BORDEAUX.
 Sodium salt of α -naphthalene-azo- β -naphthol-3 : 6-disulphonic acid.
 Soluble in water, moderately soluble in alcohol.
- 179 **Carmoisine**, *syn.* AZORUBINE.
 Sodium salt of 4-sulpho- α -naphthalene-azo- α -naphthol-4-sulphonic acid. Soluble in water.
- 182 **Fast Red E.**
 Sodium salt of 4-sulpho- α -naphthalene-azo- β -naphthol-6-sulphonic acid. Soluble in water and moderately soluble in alcohol.
- 184* **Amaranth** (Aus., Can., U.S.A.).
 Sodium salt of 4-sulpho- α -naphthalene-azo- β -naphthol-3 : 6-disulphonic acid. Soluble in water, sparingly soluble in alcohol.
- 370 **Congo Red.**
 Sodium salt of diphenyl-diazo-bis- α -naphthylamine-4-sulphonic acid. Soluble in water.
- 677* **Magenta**, *syn.* FUCHSINE, ROSEINE (Aus.).
 Mixtures of *p*-rosaniline and rosaniline hydrochlorides.
 Soluble in hot water, and in alcohol. Soluble in amyl alcohol (useful for detection in wine).
- 692 **Acid Magenta**, *syn.* ACID FUCHSINE.
 Mixture of salts of di- and trisulphonic acids of *p*-rosaniline and rosaniline. Soluble in water, almost insoluble in alcohol.
- 768 **Eosin.**
 Sodium or potassium salt of tetrabromofluorescein.
 Soluble in water and alcohol.
- 773* **Erythrosine** (Aus., Can., U.S.A.).
 Sodium or potassium salt of tetraiodofluorescein.
- 774 **Phloxin.**
 Potassium salt of tetrabromodichlorofluorescein.
 Aqueous solution fluorescent.
- 777 **Rose Bengale.**
 Potassium or sodium salt of tetraiododichlorofluorescein.
 Aqueous solution not fluorescent.

Violet

- 279 **Wool Black.**
 Sodium salt of *p*-sulpho-benzene-azo-*o*-sulphobenzene-azo-*p*-tolyl- β -naphthylamine. Soluble in water.
- 315 **Naphthol Black B.**
 Sodium salt of 6 : 8-disulpho- β -naphthalene-azo- α -naphthalene-azo- β -naphthol 3 : 6-disulphonic acid. Soluble in water.
- 463 **Azoblue.**
 Sodium salt of ditolyl-diazo-bis- α -naphthol-4-sulphonic acid.
 Soluble in water.
- 680 **Methyl Violet.**
 Mixtures of hydrochlorides of higher methylated *p*-rosanilines.
 Soluble in water and alcohol.
- 846 **Mauveine.**
 Mainly amino-phenylamino-*p*-tolyl-ditolazonium sulphate.
 Insoluble in cold water, soluble in alcohol.

Yellow

(Water soluble.)

- 10* **Naphthol Yellow S.** (Aus., Can., U.S.A.).
Potassium or Sodium salt of 2 : 4-dinitro- α -naphthol-7-sulphonic acid.
- 16* **Acid Yellow.**
Sodium salt of aminoazobenzene-di (and mono-) sulphonic acid.
The aqueous solution has a neutral action, mineral acids change the colour to a bright red, yellow being restored by the addition of alkali.
Used for colouring milk (1 in 200,000), egg powders—custard prepared for table contains about 1 in 40,000.
- 364 **Brilliant Yellow**, *syn.* PAPER YELLOW.
Sodium salt of 2 : 2'-disulphostilbene-4 : 4'-diazo-bis-phenol.
- 640* **Tartrazine** (Can., U.S.A.).
Sodium salt of 4-*p*-sulphobenzene-azo-1-*p*-sulphophenyl-5-hydroxy-pyrazol-3-carboxylic acid.
A yellow powder almost unaffected in colour by acids or alkalis.
When tartrazine is reduced sulphanilic acid is formed. Used for lemonade, etc., a common proportion being 1 in 500,000.

Yellow

(Oil soluble.)

- 15* **Aminoazobenzene.**
Aminoazobenzene hydrochloride (for fats and cheese).
- 17* **Aminoazotoluol.**
Aminoazotoluene or HCl salt (for fats, wax and margarine).
- 19* **Oil Yellow.**
Dimethylaminoazobenzene or benzene-azo-dimethyl-aniline (for oils).
- 22* **Oil Yellow A.B.** (U.S.A.).
Benzene-azo- β -naphthylamine (for oils and fats).
- 61* **Oil Yellow O.B.** (U.S.A.).
o-toluene-azo- β -naphthylamine (for oils and fats).

Other harmless colouring agents are madder, logwood, annatto, turmeric, marigold, chrysophanic acid and saffron. Naphthol green, metanil yellow, Bismark brown, and methylene blue are stated to be more or less poisonous. Certain dyes, rosaniline for example, are liable to contain arsenic, such as by the use of arsenic acid as oxidising agent, or from the use of crude oil of vitriol containing arsenic.—Kenwood.

Of the synthetic aniline dyes relatively few are considered harmless in other countries.—Final Report of the Food Preservative Committee, 1924, v. antea.

Annatto Substitute

Is a mixture of acid brown No. 1 (10 parts) and acid yellow (8 parts). *Acid brown* is the sodium salt of para-sulpho-benzene-azo-metatoluylene-diamine (4) (SO_3Na) $\text{C}_6\text{H}_4\text{N} : \text{NC}_6\text{H}_2(\text{CH}_3)(\text{NH}_2)_2$ (1.5.2.4.). A dark brown powder with occasional yellow specks dissolving easily in water. The solution has a neutral reaction and is of a dark red colour, becoming yellow when greatly diluted. Mineral acids change the solution to a bright red. Alkalis return original colour.

Used for the same purposes as the vegetable colour (has approximately 25 times the tinctorial power of the commercial extracts of the fruit, of which 1 tablespoonful is added to 30 lb. cheese, i.e., 1 part in 960) for tinting milk, butter, cheese (1 in 24,000), haddocks, etc.

Bixæ Folia, *Ph. Ned. IV* (*Bixaceæ*). The leaves of *B. Orellana*. Annatto is obtained from the seed.

Annatto Extract.—Bixin, related to *m*-xylene, is the essential colouring matter. The extract is usually strongly alkaline.

In the amount used, egg yellow, lemon yellow, and annatto substitute are thought to be harmless.—S. Rideal.

ANNATTO. A sample (rejected) gave 72.0% matter insoluble in boiling alcohol and contained 18.15% moisture. Another gave 8.5% insoluble.—Evans

Chrysoidine has been used, but there is not sufficient evidence of toxicity to justify prohibition of such colouring matters.—Mr. Neville Chamberlain.

Chrysaniline, a poisonous dyestuff, used by hawkers in some parts of the country to colour unripe oranges.—*Pharm. J.*, i/1925, 618.

Permitted colours in U.S.A. Ponceau 3R, amaranth, erythrosine, orange I, naphthol-yellow S, tartrazine, yellow AB, yellow OB, guinea-green B, light green SF yellowish, indigotin.—*Yearb. Pharm.*, 1926, 82.

For a bibliography on *heavy metals in food* and biological material compiled by T. H. Pope at the request of the Publications Committee of the Society of Public Analysts, see (I Copper), *Analyst*, 1932, 709; (II Lead), 1932, 775; (III Zinc), 1933, 30; (IV Manganese), 1933, 91; (V Mercury), 1933, 280; (VI Cobalt, VII Nickel, VIII Chromium), 1933, 340; (IX Tin), 1933, 398; (X Bismuth), *Analyst*, 1933, 607; (XI Antimony, XII Cadmium, XIII Thallium) *Analyst*, 1934, 109. (These have now been published in one compilation for the years 1921 to 1933 inclusive, but the individual references are given here for convenience).

Summary of evidence concerning alleged harmful results from taking aluminium.—J. H. Burn, *Analyst*, 1932, 428.

MOULD INHIBITION BY MEANS OF VARIOUS PRESERVATIVE SUBSTANCES

Experiments were conducted by W. H. Martindale to determine the minimum strength of **benzoic, boric, salicylic and sulphurous acids**, in aqueous solution, which would successfully inhibit the growth of the under-mentioned moulds. **Sodium benzoate** and saturated solution of **clove oil** were also included in the investigation.

Aspergillus Glaucus.

Penicillium Expansum.

Penicillium Glaucum.

Rhizopus Nigricans.

Thamnidium Elegans.

Method

10 ml. of the solutions tested were inoculated with 48-hour growths of the various moulds. The tubes were gently agitated, to ensure even distribution of the spores, and after 10 minutes 0.1 ml. was transferred to tubes of **Czapeck's medium**.

In some instances, notably *Penicillium Glaucum*, an abundant growth in 24 hours was observed, but in the results given on the next page 48 hours were allowed.

For inoculation, pure cultures were used of the moulds (48 hours old) on Czapeck's medium, since maximum active spore formation takes place during that period.

(Czapeck's medium, Brooks' modification, by courtesy of the National Collection of Type Cultures, is: magnesium sulphate 0.5, potassium dihydrogen phosphate 1, potassium chloride 0.5, ferrous sulphate 0.01, sodium nitrate 2, cane sugar 15, agar 20, water 1000. Autoclave 10 minutes at 110°.)

Control experiments were carried out in each instance, and the whole series was cultivated in daylight at a temperature of 20° to 25°. The results were as follows:—

Preservative	Mould	Strength in parts per million					Remarks
		200	500	1000	2000	3000	
Benzoic acid	<i>Aspergillus Glaucus</i> . .	+	—	—	—		Sodium benzoate 3000 p.p.m. does not inhibit growth of these moulds.
	<i>Penicillium Expansum</i>	+	+	+	+		
	<i>Penicillium Glaucum</i>	+	+	+	+		
	<i>Rhizopus Nigricans</i> . .	+	+	+	+		
	<i>Thamnidium Elegans</i>	+	+	+	+		
Boric acid	<i>Aspergillus Glaucus</i> . .	+	+	+	+		Abundant reproduction after 24 hrs. 20,000 p.p.m. does not inhibit any of the moulds.
	<i>Penicillium Expansum</i>	+	+	+	+		
	<i>Pencillium Glaucum</i>	+	+	+	+		
	<i>Rhizopus Nigricans</i> . .	+	+	+	+		
	<i>Thamnidium Elegans</i>	+	+	+	+		
Clove oil (Satd. aq. soln.)	<i>Aspergillus Glaucus</i> . .						Does not inhibit growth of moulds tested.
	<i>Penicillium Expansum</i>						
	<i>Penicillium Glaucum</i>						
	<i>Rhizopus Nigricans</i> . .						
	<i>Thamnidium Elegans</i>						
Salicylic acid	<i>Aspergillus Glaucus</i> . .	—	—	—	—		+ after 96 hrs. in 200 p.p.m. Slight growth in 500 p.p.m. in 36 hrs. Abundant growth in 200 p.p.m. in 36 hrs.
	<i>Penicillium Expansum</i>	+	—	—	—		
	<i>Penicillium Glaucum</i>	+	+	—	—		
	<i>Rhizopus Nigricans</i> . .	+	—	—	—		
	<i>Thamnidium Elegans</i>	+	—	—	—		
Sulphurous acid	<i>Aspergillus Glaucus</i> . .	+	—	—		—	Growth in 200 & 500 p.p.m. after 36 hrs.
	<i>Penicillium Expansum</i>	+	—	—		—	
	<i>Penicillium Glaucum</i>	+	+	—		—	
	<i>Rhizopus Nigricans</i> . .	+	+	—		—	
	<i>Thamnidium Elegans</i>	+	—	—		—	

Sulphurous Acid was found the most effective, 1000 parts per million (or 0.1%) being sufficient to prevent growth under ideal conditions (medium, temperature, etc.). Although the acid in this proportion successfully prevents mould growth, its use as a food preservative is limited, as the amount permissible in most cases is in the neighbourhood of 100 to 200 parts per million. v. p. 459.

Fruit Pulps. The only preservative in use is SO_2 , either as such, or rarely as calcium acid sulphite in amounts conforming to the requirements of the Regulations.

Jams. SO_2 in the pulp is dispersed by the boiling process. The resulting jam is either free or contains minute amounts, e.g., 10 parts per million (40 is the maximum permitted).

To ensure freedom from mould growth, the jam must contain at least 66% of total sugars.

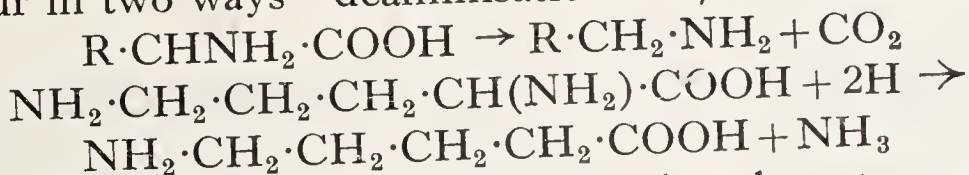
Sauces and Pickles. The vinegar inhibits moulds and yeasts. The acidity calculated as acetic acid should not be below 3%. Where this acidity is objectionable the product is "sterilised" by heating at 180°F .

PUTREFACTION BASES

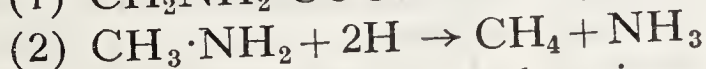
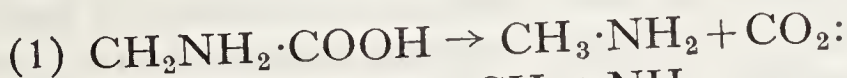
(Ptomaines)

The term "Ptomaine" was originally applied to bases extracted from corpses by Selmi. Later Briegii introduced the term "putrefaction base," which expresses the meaning more clearly, and lately the word "ptomaine" has fallen into disuse.

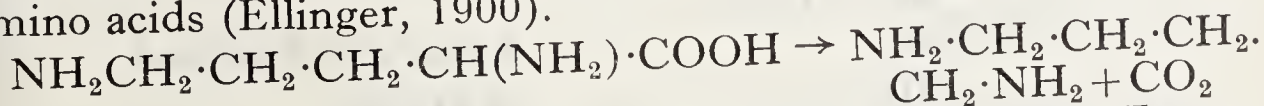
The first stage of putrefaction is the hydrolysis of proteins to amino acids, and the putrefaction base is the product of bacterial (or fungal) action on the amino acids so produced. This reaction may occur in two ways—deaminisation and/or decarboxylation.



Neuberg and Rosenberg (1907) showed that these two processes, working together, could explain the production of methane from glycine:—

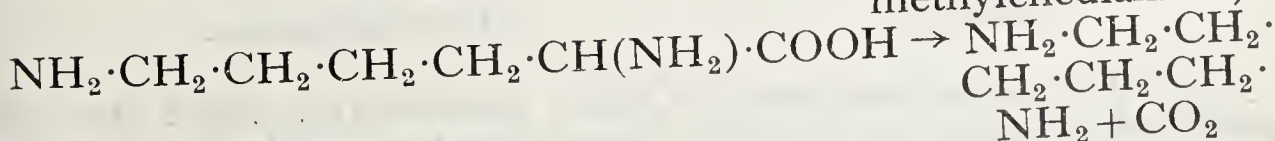


The formation of putrescine and cadaverine, the commonest of putrefaction bases, by bacterial action on ornithine and lysine respectively, provides the first examples of decarboxylation of amino acids (Ellinger, 1900).



Ornithine

Putrescine (Tetramethylenediamine)

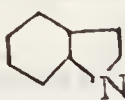
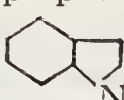


Lysine

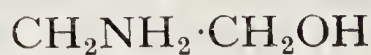
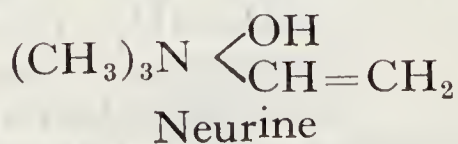
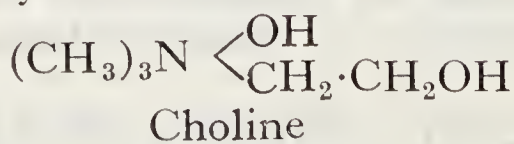
Cadaverine
(Pentamethylenediamine)

The reaction takes place much more readily under anaerobic conditions.

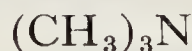
Understanding of the mechanism of this reaction has helped considerably in the recognition of putrefaction bases. Thus each amino acid can give rise to a corresponding base.

Putrefactive Base	Parent amino acid
Methylamine CH_3NH_2	Glycine $\text{CH}_2(\text{NH}_2)\text{COOH}$
Ethylamine $\text{C}_2\text{H}_5\cdot\text{NH}_2$	Alanine $\text{CH}_3\cdot\text{CH}(\text{NH}_2)\text{COOH}$
Isobutylamine $(\text{CH}_3)_2\text{CH}\cdot\text{CH}_2\text{NH}_2$	Valine $(\text{CH}_3)_2\text{CH}\cdot\text{CH}(\text{NH}_2)\text{COOH}$
Isoamylamine $(\text{CH}_3)_2\text{CH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{NH}_2$	Leucine $(\text{CH}_3)_2\text{CH}\cdot\text{CH}_2\cdot\text{CH}(\text{NH}_2)\text{COOH}$
Putrescine	Ornithine
Cadaverine	Lysine
β -Phenylethylamine $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{NH}_2$	Phenylalanine $\text{C}_6\text{H}_5\text{CH}_2\cdot\text{CH}(\text{NH}_2)\text{COOH}$
<i>p</i> -Hydroxyphenylethylamine $\text{OH}(\text{C}_6\text{H}_4)\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{NH}_2$	Tyrosine $\text{HO}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{CH}(\text{NH}_2)\text{COOH}$
3- β -Aminoethylindole  $\cdot\text{CH}_2\cdot\text{CH}_2\text{NH}_2$	Tryptophane  $\cdot\text{CH}_2\cdot\text{CH}(\text{NH}_2)\text{COOH}$
β -Iminoazolyethylamine $\begin{array}{c} \text{CH} - \text{NH} \\ \quad \quad \quad \geq \text{CH} \\ \text{C} - \text{N} \\ \\ \text{CH}_2\cdot\text{CH}_2\cdot\text{NH}_2 \end{array}$	Histidine $\begin{array}{c} \text{CH} - \text{NH} \\ \quad \quad \quad \geq \text{CH} \\ \text{C} - \text{N} \\ \\ \text{CH}_2\cdot\text{CH}(\text{NH}_2)\text{COOH} \end{array}$

A few putrefaction bases have their origin in substances other than the amino-acids of proteins. Lecithin and other phosphatides are broken down to yield a restricted number of basic substances. In fact only two primary scission products are known—choline and aminoethyl alcohol—although these, in their turn, can yield secondary products of decomposition—neurine and trimethylamine.



Aminoethyl alcohol



Trimethylamine

It will be seen that most of these putrefaction bases are comparatively simple compounds which would be unlikely to produce the effects known as ptomaine poisoning. Again, they often occur at a comparatively late stage in putrefaction, and by the time of their production in any quantity the food would be uneatable.

Thus, food poisoning cannot be due to putrefaction alone and is probably of bacterial origin. *See also Food Poisoning, Bacterial*, this vol., p. 516, and *Botulism*, Vol. I, p. 1034.

Symptoms of poisoning are those of gastro-intestinal irritants, but they may resemble those of atropine poisoning. Dryness of the tongue, thirst, dilated pupils, debility, with probably rigors, offensive diarrhœa, high temperature and sickness with convulsions may occur.

Tyrotaxon occurs in stale cream, cheese, milk products; causes vomiting, purging, rapid pulse, dyspnœa, depressed temperature and prostration.

Antidotes. Give emetics and castor oil, then stimulants. Amyl nitrite, strychnine, digitalis, caffeine, sal volatile, tannic acid, and atropine hypodermically. For **fish poisoning** give potassium chlorate or liquor ammoniæ acetatis, also tinctura capsici and spiritus chloroformi.

Outbreak of illness due to tinned meat in Carlisle. The meat (American corned beef) reported as bacteriologically unfit for food. It was proved to be contaminated, previous to, or at the time of canning in America.—*Lancet*, ii/1910, 1613.

NOTES ON WATER ANALYSIS

Sampling

About 2 litres of water are required for complete analysis. The sample should be taken in a thoroughly clean Winchester which has been rinsed out several times with the water in question. If tap water is concerned allow the water to run for several minutes and then fill the bottle completely; if the sample is to be taken from a river, lake, well, cistern, etc., immerse the Winchester completely and then withdraw the stopper. Examine the water as soon as possible after sampling.

Physical Examination

Odour: No odour should be perceptible even on warming.

Turbidity: Note whether it is bright and clear or opalescent or turbid. If turbidity is pronounced, filter 1 litre through a weighed Gooch crucible, dry at 100° , weigh and express the result in parts per 100,000.

Colour: Note in a 100 ml. Nessler tube, comparing with distilled water. A yellow tint may indicate organic contamination.

Conductivity: The greater the saline content the higher the electrical conductivity. The E.C. of a very soft water may be ten times that of distilled water, while that of a hard water may be 300 times as great. The conductivity at 20° , expressed in gemmhos (1.0×10^{-6} reciprocal ohm) divided by 20 roughly approximate to the degrees of hardness.

The "Dionic" Water Tester (manufactured by Evershed and Vignoles, Chiswick, W.4), devised by Digby and Biggs, is a convenient portable apparatus suitable for such determinations. It consists of a special U-tube, arranged so that the water can circulate through, supplied with platinum electrodes fed by a small continuous current dynamo turned by hand. The conductivity meter reads directly in reciprocals of 1 megohm and the scale is graduated from 0 to 2000. The only correction is for temperature.

This apparatus can be used for periodical examination of water supply; any abnormal variation would suggest a search for the cause, which might be the influx of an objectionable contamination.

Chemical Examination

Total Solids. Heat a clean, platinum basin of about 70 ml. capacity to 180° for fifteen minutes, cool in a desiccator and weigh. Transfer to the basin, in successive amounts, a quantity of the sample varying from 100 ml. to 500 ml. and evaporate to dryness on a steam bath. On completion, wipe the outside of the basin and dry to constant weight at 180° .

NOTES. The amount of sample used should be such that the residue weighs not less than 0.02 g. Drying at 180° is adopted.

to avoid discordant results due to retention of water of crystallisation; even at this temperature CaSO_4 retains 1 molecule. In reporting results, the temperature of drying should always be stated. Ignition of the residue may yield an indication of the presence of organic matter. The ignited residue may be analysed qualitatively to detect the presence of Na, K, Ca, Mg, Fe, Mn, Pb, and Zn.

Total solids should not exceed 50 parts per 100,000.

Ammonia. “*Free*” or *saline ammonia*, usually in combination with carbonic acid.

Apparatus required: 1 litre distillation flask with the delivery tube bent down at right angles and fitted by means of a cork into an upright, double surface condenser which itself dips into a 50 ml. measuring cylinder used as a receiver. The whole of the apparatus must be chemically clean.

Place 500 ml. of the sample, together with 1 g. of freshly ignited Na_2CO_3 , in the flask and distil fairly slowly and regularly over a free flame, collecting three 50 ml. portions in separate measuring cylinders. Nesslerise the *second* fraction first with standard ammonium chloride solution (1 ml. \equiv 0.01 mg. NH_3). If less than 2 ml. of the standard is required, the whole of the first portion may then be treated similarly; if more than 2 ml. is used, half of the first portion should be diluted to 50 ml. and then Nesslerised. The total volume of ammonium chloride used for the whole distillate is equivalent to the “free” ammonia in 500 ml. of sample; calculate as parts per 100,000.

Albuminoid Ammonia. This determination serves only as a rough guide to the quantity of organic matter in solution, as only a variable amount of the total organic nitrogen is recovered as ammonia.

Dissolve 4 g. of potassium permanganate and 100 g. of sodium hydroxide in about 700 ml. of water and boil until the volume is 500 ml. Add 50 ml. of this solution to the water remaining in the flask after the determination of free ammonia, add some pieces of ignited porous pot to prevent bumping, and continue the distillation, collecting a further four 50 ml. fractions. Nesslerise the whole of this distillate, beginning with the last portion, and calculate the amount of albuminoid ammonia per 100,000.

NOTES.—More than 0.005 part per 100,000 of free ammonia indicates possible pollution; more than 0.01 part per 100,000 of albuminoid ammonia is rarely encountered in satisfactory water.

Nessler’s Reagent for Ammonia. *Syn.* SOLUTION OF POTASSIO-MERCURIC IODIDE.

Dissolve potassium iodide 7 and mercuric chloride $2\frac{1}{2}$, in distilled water 160. To this add more of the mercuric chloride in solution until the precipitate no longer disappears on well stirring, and a slight permanent precipitate remains. Then add sodium hydroxide 24, dissolve, add a little more solution of mercuric chloride and distilled water, *q.s.* to 200.

Nessler’s Reagent (Richmond’s Formula)

A very sensitive reagent may be made by mixing a solution of 17.5 g. of potassium iodide in 100 ml. of water with 15 g. mercuric chloride in 300 ml. of water, thoroughly washing precipitate by decantation, and dissolving in 17.5 g. of potassium iodide in 100 ml. of water. A few drops of mercuric chloride solution are then added until a precipitate insoluble on shaking is formed; the mixture is diluted to about 500 ml., cooled in ice and mixed with a solution of 105 g. sodium hydroxide in 250 ml. The mixture is made up to 1 litre and allowed to settle.—H. D. Richmond, per *Pharm. J.*, ii/1925, 394. *It is claimed to be far more delicate than the B.P. ’32 formula. For a further modification, see p. 325.*

Estimation of Ammonia in Water in presence of Hydrogen Sulphide. The presence of hydrogen sulphide in a water interferes with the Nessler test. If the amount of ammonia be large the sulphide may be precipitated with a zinc or lead salt and the ammonia can then be estimated directly by the Nessler reagent. If the amount is small it is best to add to 500 ml. of the water, a measured quantity of N/1 sulphuric acid and distil 100 ml.—this completely removes

H_2S . A volume of N/1 NaOH equal to that of the H_2SO_4 used is now added. The water is again distilled until 200 ml. have been collected and the Nessler test is applied to the distillate.

Chloride. Place in a white porcelain basin 100 ml. of the sample and 1 ml. of a 5% solution of potassium chromate. Titrate with standard solution of silver nitrate (1 ml. \equiv 1 mg. Cl.), with frequent shaking, to a faint, permanent reddish-brown colour. Then titrate with the sample until this colour is *just* destroyed (up to 20 ml. may be required). The amount of silver nitrate used is equivalent to the chloride in 100 ml. plus half the extra water used in the second titration. If the sample is acid, add a little sodium bicarbonate; if it contains small amounts of hydrogen sulphide add a crystal of zinc sulphate before titration. The reagent must be Cl-free. The average content is about 2 parts per 100,000, though frequently one finds a content of 5 to 15 parts per 100,000. It should be remembered that urine and sewage are, comparatively speaking, highly charged with chlorine—this enables the analyst to determine whether a high albuminoid ammonia content is attributable to sewage or vegetable influence. *Per contra*, almost entire absence of chlorides, coupled with excess of albuminoid ammonia and little free ammonia, suggests vegetable contamination of a dangerous character. One frequently obtains waters for examination with an exceedingly high Cl-content in conjunction with an almost total absence of organic impurity. Such waters, though “saline,” are suitable for drinking purposes.

Oxygen Absorbed. Pure waters absorb very little oxygen, whereas those that are polluted may absorb comparatively large quantities, and hence this determination, whilst difficult to interpret in terms of type or quantity of organic matter, has considerable value.

Place 250 ml. of the sample in a clean stoppered bottle, warm to 37° , add 10 ml. of N/80 potassium permanganate, 10 ml. of 25% H_2SO_4 , and keep at 37° for three hours. Cool quickly, add potassium iodide and titrate the excess of permanganate with N/250 sodium thiosulphate recently standardised. From the amount of permanganate decomposed by the water calculate the parts of oxygen absorbed per 100,000 (1 ml. N/80 solution of potassium permanganate \equiv 0.1 mg. of available oxygen).

NOTE: Different laboratories use vastly different times and temperatures in this determination: comparisons are valid only if based upon figures obtained under identical conditions. The figures obtained should be considered in relation with those for albuminoid ammonia and should be repeated if the ratio of oxygen absorbed to albuminoid ammonia differs materially from 10 to 1.

Nitrites. Rarely present in natural waters except in minute traces, and a qualitative test is all that is required.

ILOSVAJ'S REAGENT. Dissolve 0.1 g. of α -naphthylamine in 120 ml. of boiling distilled water, cool and add 30 ml. of glacial acetic acid. Dissolve 0.5 g. of sulphanilic acid in 120 ml. of distilled water and 30 ml. of glacial acetic acid.

Mix the two solutions and keep in a stoppered bottle. If any colour develops on keeping, add a little zinc dust, and filter.

Test. Add 2 ml. of the above reagent to 50 ml. of the sample in a Nessler cylinder. The appearance of a pink colour in a few seconds denotes more than a trace; if it takes 10 minutes to develop, only a minute trace is present. Alternatively, the amount present may be determined by conducting the test under Nesslerising conditions, using a standard solution of sodium nitrite as a standard.

Nitrates. A determination of nitrates should always be made. First apply a qualitative test by carefully mixing 1 ml. of the sample with 3 ml. of nitrogen-free sulphuric acid; cool and add brucine; a bright red is obtained if 10 parts per 100,000 are present—a pale rose if only 0.1 part.

Place from 10 to 100 ml. of the sample, depending upon the amount of nitrate present (10 ml. if 1 part per 100,000) in a small flask with a few grammes of thoroughly washed zinc-copper couple, acidify with a few drops of 10% hydrochloric acid and heat at 37° for one hour. Place about 300 ml. of distilled water in the distillation apparatus used for the determination of ammonia together with 1 g. of ignited sodium carbonate, and distil 50 ml. to remove all ammonia. When the reduction is complete, pour the water from the copper-zinc couple, together with the rinsings of the couple with distilled water, into the flask and distil two fractions of 50 ml. Determine the amount of ammonia in the fractions by Nesslerising and calculate the number of parts of nitrate (as NO_3) in 100,000.

Hardness. The “degrees” of hardness refer to the soap-destroying power, 1° being roughly equal to that of 1 part of calcium carbonate, or its equivalent in other calcium or magnesium salts, in 100,000. “Temporary” hardness is that which disappears on boiling and is due to bicarbonates; “permanent” hardness is that which remains after boiling. No diminution in hardness occurs on boiling unless more than 2° is due to bicarbonates, as calcium carbonate is soluble to that extent. As the hardness is due to bicarbonates, carbonates, sulphates and chlorides of calcium and magnesium, the correspondence between degrees and the content of these salts is only approximate.

Total Hardness. Place 100 ml. of the sample in a 200 ml. stoppered bottle and titrate with standardised soap solution until, after shaking vigorously, the lather persists for five minutes, the bottle being laid on its side. Subtract 1 ml. from the reading, as this amount is required to produce a lather in water free from salts: the net number of millilitres of soap solution used is equal to the degrees of hardness. If more than 15 ml. of soap solution is required, repeat the titration, using 50 ml. of sample diluted to 100 ml. with distilled water: the degrees of hardness will then be twice that of the dilution.

Temporary Hardness. Boil 100 ml. of the sample in a flask of resistance glass for 30 minutes, replacing that lost by evaporation from time to time with distilled water. Allow to cool, filter, make up to 100 ml. and determine the degrees of

Permanent Hardness by titration with soap. Total Hardness minus Permanent Hardness equals Temporary Hardness.

Standard Soap Solution. Dissolve 10 g. of hard soap in 1 litre of 45% alcohol. To standardise this solution, dissolve 1 g. of calx spar in slight excess of hydrochloric acid, evaporate to dryness and dissolve the residue in sufficient distilled water to make 1 litre. Dilute 10 ml. of this solution to 100 ml. with distilled water and titrate with the soap solution. Adjust the soap solution until 11 ml. is the amount required.

Degree of hardness (total)—

5°	Soft waters
15°	Hard waters
Over 20°	Very hard

If the hardness is over 30° the water is unfit for general purposes.

HARD v. SOFT WATER. Tabulated results of examinations give no indication whatever that the hardness or softness of waters has anything to do with the prevalence of or mortality from cancer, phthisis or enteric; similarly the character of water supplies in this country has nothing to do with the general death rate.—J. C. Thresh, *Brit. med. J.*, ii/1913, 1058.

CHALKY WATER. Public (and often other) opinion is to the effect that chalky drinking waters may be responsible for a variety of complaints, e.g., gout, rheumatism, calculus, constipation, biliousness, dyspepsia, eczema, goitre and arteriosclerosis. P. G. Lewis has stated: "There is no evidence that hard water has any bad effect—on the contrary, the evidence is all the other way."

Poisonous Metals. Concentrate the water 5 times after acidifying with a few drops of hydrochloric acid. Add ammonia and hydrogen sulphide solutions. A darkening in colour shows the presence of Pb, Cu, or Fe, but not Zn. Divide into two portions and acidify one part with hydrochloric acid. The disappearance of the colour indicates the absence of Pb and Cu. To the second part add potassium cyanide solution—the persistence of the colour shows that it is due to the presence of Pb. Confirmatory tests should always be employed.

Iron. Acidify 50 ml. of sample with sulphuric acid and add potassium permanganate solution until a slight pink colour persists. Filter and add solution of potassium ferrocyanide solution. If iron is present, a blue colour is formed.

Zinc. If present, an opalescence will be noticed in the above test.

A pure soft water may exert a solvent action upon zinc (e.g., galvanised kettles), and may become dangerous to health.

Zinc in small quantities is found in soft waters passing through galvanised iron pipes. From the health aspect and danger of poisoning, it can be ignored.—J. C. Thresh, *Lancet*, ii/1915, 1098. See also Park Prewett, *Brit. med. J.*, 1/1915, 80.

Copper. If present, a reddish-brown colour is obtained with the ferrocyanide test.

Lead. Acidify 100 ml. of sample with acetic acid and concentrate to 5 ml. Filter and add a crystal of potassium chromate. In presence of lead, a precipitate of lead chromate is obtained. See also details for army purposes, p. 489.

Electrolysis in lead water pipes, owing to leak of 1·8 volts in earthed return of electric cable, has resulted in contamination of the water.

EXCESSIVELY PURE WATER may be solvent of lead in service water. It is recommended to harden it by adding lime.

PEATY WATERS owing to *acidity* often dissolve lead from main pipes in the form of lead hydrogen carbonate. On standing or on boiling, it is thrown out with the calcium carbonate.

LEAD ABSORPTION from drinking water, 120 cases.—*Lancet*, ii/1914, 213.

Calcium and Magnesium. Acidify 200 ml. of sample with 1 ml. of diluted hydrochloric acid and concentrate to 50 ml.; make alkaline with ammonia, add 2 ml. of saturated solution of ammonium oxalate and heat for one hour. Collect

and thoroughly wash the precipitate, dissolve in dilute sulphuric acid and titrate with N/100 potassium permanganate (1 ml. \equiv 0.0002 g. Ca). Magnesium is determined in the filtrate and washings from the above estimation after making the volume up to 100 ml. Of this, take a volume containing approximately 0.5 mg. of magnesium (say 25 ml.) and dilute to 100 ml. in a Nessler glass; add 2 ml. of ammoniacal solution of ammonium phosphate and agitate for 2 minutes with a plunger. Compare the opalescence with that produced by 100 ml. of a solution of magnesium sulphate of known concentration treated similarly.

Fluorine. Fluorine may be determined colorimetrically using a reagent made by mixing 3 ml. of a solution of zirconyl chloride (3.53% *w/v* of $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$) with 1 ml. of 1% aqueous sodium alizarin monosulphonate and diluting with water to 200 ml. To 50 ml. of the sample in a Nessler glass add 2.5 ml. of hydrochloric acid, mix, and add a sufficient quantity of the reagent to give a very faint pink tinge remaining after standing for 10 minutes. For fluorine contents below 1 part per million, 2 ml. of reagent is sufficient; for 5 parts per million, 4 ml. of reagent is required, the tint being orange. The colour produced is matched against standards obtained by treating similarly and at the same time solutions containing 1, 2, 4 and 8 parts per million of fluorine (as fluoride).—Guy Barr and A. L. Thorogood, *Analyst*, 1934, 378.

Fluorine and Mottled Teeth. A daily intake of 0.1 to 0.15 mg. of fluorine per kilogramme of body-weight is sufficient to cause mottling. Sufficient fluorine may be removed from water to render it harmless by coagulation with aluminium sulphate and filtration.—*Lancet*, ii/1934, 34.

About 90% of the children born and bred in Maldon, Essex, were found to have mottled teeth due to the presence of between 4.5 and 5.5 parts per million of fluorine in the water supply. The essential condition is that the water should be drunk during the years the teeth are being formed. When once through the gums, the condition could not be influenced one way or the other.—N. J. Ainsworth, *Analyst*, 1934, 380.

Iodine. The quantity of iodine in natural waters is infinitesimal although deep wells may contain more than surface water. No definite conclusions have been reached concerning the correlation between the absence of iodine in water and the prevalence of endemic goitre. It has been observed that the iodine content of water in Michigan is inversely proportional to goitre incidence and a similar relationship has been shown to exist in New Zealand between iodine content of soil and goitre incidence. On the other hand, waters of high calcium content may interfere with iodine absorption and thus contribute a positive factor in the incidence of goitre (see Leader, *Brit. med. J.*, i/1931, 361). The earth's crust and not the sea is held to be the storehouse of iodine and heavy cropping of the soil tends to deplete it of iodine (*Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 123, 1929).

The question has received much attention and the reader is referred to Vol I for further information on this subject, and for details to the following literature:—

Iodine in Nutrition : a Review of Existing Information. J. B. Orr and I. Leitch, *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 123, 1929 and No. 154, 1931; O. P. Kinball, *J. Amer. med. Ass.*, ii/1931, 1877; *Endemic Goitre in Switzerland.* A review of recent contributions to its aetiology, incidence and prevention. Olesen, *Publ. Hlth. Rep., Wash.*, 1933, 651.

See also last edition of this volume, p. 422 *et seq.*, in which the methods used and the results obtained by W. H. Martindale are described.

Interpretation of Results.

Before a final judgment can be delivered upon any water there have to be taken into consideration (1) its geological history (2) the rainfall before and after collection, (3) the method of storage and distribution, (4) the surface drainage, and (5) a bacterial examination. A water which chemically is organically pure may be bacterially contaminated, and on the other hand a bacterially pure water may be chemically dangerous or suspicious.—Purvis, *Pharm. J.*, ii/1910, 149.

DISTILLED WATER

Bacteriological Notes

Some years ago the opinion was expressed that saline fever occurring after injection of Salvarsan was due to dead bacteria in the saline solution used as a solvent of the arsenical compound—the effect was thought to be attributable to protein shock.

Donald's method of counting bacteria in water includes the dead bacteria whilst the usual cultural methods eliminate them. Extraordinary differences are recorded. A water, for example, grown on agar for two days at 37° showed no organisms. On gelatin at 18° to 22° for 10 to 14 days it showed 160 to 300,000 per millilitre, whilst by Donald's method there were 1,500,000 per millilitre.

Drops of the water from special capillary pipettes are used. Bacteria contained in the water are counted by evaporating and staining on microslides. By the method it was shown that distilled water kept for 3 weeks may develop as many as 15,000,000 bacteria per millilitre.—*Lancet*, i/1913, 1447.

Tap water always, and about 50% of all distilled waters, produce a rise of temperature when injected intravenously into rabbits. This fever is due to a bactericidal product formed by a specific bacterium which contaminates the water.—F. B. Siebert and H. G. Wells, *J. Pharmacol.*, March 1924, 154.

Experiments with Distilled Water. W. H. Martindale made an investigation to determine to what extent bacteria may *increase* in distilled water on standing. 500 ml. of fresh distilled water were exposed in a flask and counts made in the usual manner periodically. Examination at the commencement showed *the water to be sterile*.

After 3 days there were 111 organisms per ml. capable of growth on gelatin at 18°

10	"	"	52,000	"	"	"	"	"	"
15	"	"	3,800,000	"	"	"	"	"	"

At this time there was only one organism per 2 millilitre capable of growth on nutrient agar at 37°.

These results show the remarkable contamination in distilled water which may occur by air organisms. Whilst demonstrating the importance of fresh distilled water, the relative absence of pathogenic organisms is also of interest.

Ordinary chemical tests failed to detect any difference in the water either at the commencement or end of these experiments.

Distilled water has been advised as a **therapeutic agent** injected in dose of 6 to 8 ml. for syphilitic ulcers, the theory being that increased surface tension has a good deal to do with beneficial results of injections.

The use of triply distilled water in the preparation of solutions for intravenous administration is not necessary, but the use of freshly (and properly) distilled water is essential.—Elsen and Stillman, *J. Amer. med. Ass.*, i/1933, 1326. Lewisohn and Rosenthal, *ibid.*, 1793.

Bacteriological Examination

It should be emphasised that the bacteriological examination of water should only be attempted by those who have had training and experience in this branch of work.

*See also *Rep. publ. Hlth med. Subj., Lond.*, No. 71, 1934, and *Lancet*, i/1934, 1297.

The enumeration of the bacteria present is not so important as the determination of the species. Many bacteria are natural to water and quite harmless, but those which have their origin in sewage or manure are always dangerous.

Results should be considered in relation to the history and geological source of the sample. The waters from deep sources have been subjected to a natural process of filtration and are often purer than surface waters but in some formations, such as chalk, fissures develop which render the filtration insufficient.

Sampling. The sample should be taken in a sterile bottle of about 2 litres capacity. If tap water is concerned allow the water to run for several minutes and then fill the bottle completely; if the sample is to be taken from a river, lake, well, cistern, etc., immerse the bottle completely and then withdraw the stopper. Examine the water as soon as possible after sampling; the lapse of time should never be greater than 12 hours.

It is important to know whether the water, e.g., a well, has been recently disturbed by cleaning out or pumping.

To prevent increase in number of bacteria it is customary to pack the bottle in ice for transmission by rail, etc. Unless so packed there is a chance that saprophytic organisms may multiply at the expense of organisms indicative of pollution.

Enumeration of Bacteria. Prepare agar and gelatin plates with varying quantities of the specimen, e.g., 1.0, 0.1 and 0.001 ml., and incubate the former at 37° for 24 hours and the latter at 22° for 72 hours. The more plates prepared the greater the accuracy, but three of each is a reasonable number. The amount of sample used depends upon the purity of the sample; a very pure water might require the use of 3 ml. The colonies may be counted by drawing sector lines with a paraffin pencil through the petri dish, counting one section, and multiplying out to obtain the number of bacteria in the entire amount of water taken for examination. *Pakes' Discs* are employed in a similar manner. To obtain accurate results it is important to add the melted gelatin or agar medium to the specimen of water, and not the water to the medium. This procedure ensures better mixing.

The plates should be examined at intervals, and if liquefying organisms are numerous (which suggests sewage pollution) the examination has often to be concluded in a shorter time than would be necessary where such are not present.

Cultivation on gelatin at 22° enumerates the bacteria present normally in the water, whilst the body temperature (37°) will be more suitable for excremental organisms derived from, or pathogenic to, the animal body.

It is no longer considered of great importance to count the number of organisms in water, but individual search should be made for various sewage-pollution organisms, e.g., *B. coli communis*, *B. typhosus*—especially the *B. coli* group—*Vibrio cholerae*, *B. proteus*, *B. enteritidis sporogenes* Klein, and streptococci.

B. coli communis

The entire problem turns on determining whether pollution with sewage has occurred, indicated usually by the presence of the *B. coli* group of organisms. Acid and gas production in **MacConkey's Litmus Bile Salt Glucose Broth Medium** gives presumptive evidence of the presence of *B. coli*, *B. paratyphosus*, *B. enteritidis*—but excluding *B. typhosus* and the dysentery organisms. These latter produce acid formation only (without gas) in this medium.

Another step is to employ the MacConkey medium made with **lactose** instead of glucose—this forms a useful corroboration for *B. coli*—this organism gives acid and gas whereas none of the others do so. In tabular form the matter may be stated as follows:—

		Glucose	Lactose	Motility	Gelatin	Litmus Milk. 3 days	Indol.
<i>B. coli communis</i> A.G.	A.G.	+	—	A.C.	+	
<i>B. typhosus</i> A.	—	+	—	A.	—	
<i>B. paratyphosus</i> A.G.	—	+	—	Alk.*	—	
<i>B. enteritidis</i> (<i>Gaertner</i>)...	A.G.	—	+	—	Alk.	—	
<i>B. dysent.</i> (<i>Shiga</i>) ...	A.	—	—	—	Alk.	—	
<i>B. dysent.</i> (<i>Flexner</i>) ...	A.	—	—	—	Alk.	+	
<i>B. Morgani</i> No. 1 ...	A.G.	—	+	—	Alk.	+	

A = Acid. G. = Gas. C. = Clot. — under gelatin means non-liquefaction.
* *Vide* also Eyre, *Bact. Technique*, for *B. paratyphosus*, *A* and *B*.

The method used aims at the determination of the smallest quantity of water which will give a positive reaction followed by the application of a number of confirmatory tests for *B. coli*. Varying quantities of water are used for each test, in order to obtain a series which contains both positive and negative results. Different dilutions of the following special broth are prepared so that preparations made with varying quantities of the sample will all have approximately the same concentration: 1 of broth and 2 of a mixture of sample and freshly distilled water.

MacConkey's Glucose Broth

Sodium taurocholate	1.59 g.
Dextrose	1.59 g.
Peptone	6.09 g.
Water, distilled, to	100 ml.

Boil for 20 minutes, adjust to pH 7.5 with N/1 NaOH, reboil and add sufficient litmus to produce a decided colour on dilution with two parts of water. This broth is also prepared using lactose instead of dextrose.

The exact mode of procedure for the detection of acid and gas formation is as follows:—

Examination of 50 ml. of the water. Place 50 ml. of a mixture of 2 parts broth and 1 part distilled water in a 100 ml. flask containing a small inverted test tube rendered bubble-free. The whole is then plugged with sterile wool and sterilised at 100° for 20 minutes on 3 successive days. This has to be made ready before receipt of the specimen. 50 ml. of the sample to be examined is introduced with aseptic precautions.

The same procedure is gone through with the *lactose* preparation.

Examination of 20 ml. of the water. Take 10 ml. of broth in a 6×1 in. test-tube containing a small inverted test-tube rendered bubble-free and add 20 ml. of sample after sterilisation.

Examination of 10 ml. of the water. Take 10 ml. of a mixture of 2 parts of broth and 1 part of distilled water and treat similarly.

Examination of 5 ml. of the water. Take 10 ml. of equal amounts of broth and distilled water.

Examination of 2 ml. and less. Take 1 part of broth and 2 parts of distilled water.

All the tubes prepared are incubated at 37° for 48 hours, and the production of turbidity, acidity and gas indicates the presence of *B. coli*.

Subsequent to these results inoculate Neutral Red Bile Salt Agar plates with loopfuls from the cultures in the bottles—using a “spreader” made with a piece of glass rod $\frac{1}{8}$ inch diameter with an end bent at right angles to the handle and about 1½ inches long.

After incubating for 24 hours pick out with a platinum loop colonies resembling those of *B. coli*, and inoculate sloped agar tubes, *thence* peptone water for the Rosindol reaction and Indol reaction—also litmus milk for the “Acid and Curd,” and examine a fresh broth culture for motility.

The plate cultures are incubated further to observe fluorescence, if any.

Rosindol Reaction (Ehrlich's). *Syn. Böhme's Indol Test.* To 10 ml. of a 48-hour peptone water culture add 5 ml. of the following solution:—

<i>p</i> -Dimethylaminobenzaldehyde...	1
Alcohol, 96%	95
Concentrated hydrochloric acid	20

and then 5 ml. of saturated aqueous potassium persulphate solution. Shake well. According to MacConkey 1 ml. of each solution is sufficient. Pink colour in a few minutes = +. In some cases the persulphate need not be added. The pink colour is soluble in amyl alcohol—a little of which should be added, especially in doubtful cases. At least 48 hours' growth should be allowed; in some cases 6 to 8 days are required.

Indol Reaction. To 5 ml. of the (6 or 7 days) peptone water culture add 1 ml. of concentrated sulphuric acid and then 1 ml. of 0.02% sodium nitrite. Pink colour indicates indol production (some organisms, e.g., cholera vibrio, do not require the sodium nitrite—hence the test may be done in two stages). It may be necessary to incubate for 8 days or more before conducting the test.

The data in question, together with the production of fluorescence in the colonies in **Rebipel Agar**, *Syn. MacConkey's Neutral Red Bile Salt Agar*—which has the composition:—

Agar and peptone white	aa. 30 g.
Lactose	15 g.
Sodium taurocholate	7.5 g.
Tap water	1500 ml.
Solution of neutral red, 1%	7.5 ml.

constitute the “**Flaginac**” reaction which is typical of *B. coli*.

This word is made up to show the reactions on these media and is applied to organisms, e.g., *B. coli*, which will respond to all:—

- fl: fluorescence in neutral red.
- ag: acid and gas formation.
- in: indol in peptone water.
- ac: acid and clot in litmus milk.

Neutral Red, $C_{15}H_{16}N_4$ (*Syn. Toluylene Red*), is chemically dimethyldiaminoethylphenazine hydrochloride. It is readily soluble in alcohol and in ether.

The following may be regarded as decisive tests for *B. coli*. (1) Acid and curd in litmus milk; (2 and 3), motility and indol in peptone water; (4) negative to Gram's stain; (5) no liquefaction with streak cultures on gelatin; (6) fluorescence on rebipel agar; (7, 8 and 9) fermentation of sucrose, mannite and dulcitol respectively.

A thorough investigation of the source and history of a water

under examination is necessary—this is more important than laboratory diagnosis. To ascertain the *origin* of the organism is found—whether from sewage or other human source, cattle, cultivated lands, etc.

The presence of **sulphur bacteria**, *Beggiatoa alba*, which are readily identified, may be used for detecting sewage pollution, in place of a *B. coli* count.—Prof. Davis Ellis, *Pharm. J.*, ii/1926, 308.

Pathogenic Bacteria. Thresh states that “the search for pathogenic bacteria, such as typhoid-paratyphoid-salmonella bacilli, in water is beset with difficulties, and is rarely successful.” “Water supplies which naturally, or after treatment, are practically free from *B. coli* can safely be considered innocent of spreading either typhoid, salmonella or dysentery infection.” The isolation of *B. typhosus* involves a concentration by flocculation with aluminium sulphate, followed by centrifuging or by filtration through a suitable filter. The next stage consists in the culture of the bacteria in a medium favourable to the growth of the typhoid-paratyphoid bacilli and inhibitory to others. Final identification rests upon the determination of the morphological and biochemical properties of the cultures obtained. Sir A. Houston (*Rep. metrop. Wat. Bd.*, 1930) states that Wilson’s researches have simplified the search for these organisms.

Wilson’s Sulphite-Bismuth Medium: Dissolve 6 g. of bismuth ammonio-citrate scales in 50 ml. of boiling distilled water and neutralise with about 2 ml. of 10% solution of sodium hydroxide. Mix with a solution obtained by boiling 20 g. of anhydrous Na_2SO_3 in 100 ml. of water to which, whilst boiling, 10 g. of anhydrous Na_2HPO_4 have been added. When cool, add 10 g. of glucose dissolved in 50 ml. of boiling distilled water and add 20 ml. of this preparation to 100 ml. of a hot melted 3% nutrient agar, then 1 ml. of 8% aqueous ferrous sulphate solution and finally 0.5 ml. of 1% solution of brilliant green in distilled water. Pour into petri dishes and inoculate the surface when set. *B. typhosus* and *B. paratyphosus* appear as flat, black colonies, the former within 24 hours, the latter within 48 hours.—Wilson, *Brit. med. J.*, ii/1933, 561.

Other Indications of Pollution

Streptococci are numerous in fæces, are not found in pure water and do not multiply outside the human body. They can be recognised by microscopic examination of a hanging drop preparation of the primary culture in MacConkey’s broth after 48 hours’ incubation.

B. Welchii and relatives, the spore-producing, anaerobic bacteria, similarly indicate contamination with manure or sewage. Thresh recommends the use of a test for the spores of these organisms consisting of adding varying quantities of the sample to skimmed milk, covering the surface with wax melting at about 45°, heating to 80° for 15 minutes to kill organisms other than spores, and finally incubating at 37° for 4 days. If positive, the so-called “stormy fermentation,” production of acidity, clot, and gas, occurs during the incubation period; the greater the pollution the earlier the reaction.

Vibrio Cholerae. To detect: inoculate peptone water, preferably in an Erlenmeyer flask with 100 ml. of the water. Incubate and test for indol production and search for typical comma-shaped organisms, which are actively motile and decolourised by Gram’s method. Test further with usual laboratory media and also conduct serum agglutination test.

The above method, somewhat modified, used for cultivation. Identification by motility, cholera red reaction, nitroso indol, Ehrlich’s rosindol reaction, flagella staining, and agglutination test.—*Lancet*, i/1913, 1377.

B. Proteus. The ordinary laboratory media and methods may be employed for the various types of *Proteus*.

Bacillus Enteritidis Sporogenes. Add to a fresh milk tube 1 ml. of the water or a small quantity of the “concentrated” water. Heat to 80° for 2

minutes to kill off other organisms, excepting spores of the organism searched for (Kitasato's method): grow in Buchner's tube, i.e., in an atmosphere of nitrogen for 24 to 36 hours. If result be separation of milk, stringy curd, and excessive whey, test for pathogenicity on guinea-pig. The animal succumbs within 36 to 48 hours (if very virulent in 24). Post-mortem signs: bloody œdema at seat of inoculation, offensive odour, hair of animal easily detached. Films stained by Gram's method from œdema fluid show typical non-sporing organisms. To test further, a blood serum tube is inoculated from the œdema fluid and incubated under anærobic conditions. The medium is eventually liquefied by the organism, and films prepared from this show the typical sporing organism of Klein.

Leptospira Icterohæmorrhagiæ found in London tap water.—*cf.* pp. 482 and 626.

(For a full treatment of the subject the reader is referred to "*The Examination of Waters and Water Supplies*," by Thresh, Beale, and Suckling; 4th Edition, 1933, J. and A. Churchill, London.)

BACTERIOLOGICAL REPORTS ON WATERS

If *B. coli* forms a considerable proportion of the total number of organisms present there is great reason to suspect sewage pollution of human or other animal origin.

The following is a brief résumé of the customary standards:

Generally speaking, a water containing B. coli in 50 ml. but not in less is quite good if the count of total bacteria and the chemical analysis are good. See also filtered London Lea River water, postea.

Wells, Shallow and Surface. If chemical results and surroundings are bad, even if *B. coli* be absent from a large volume of the water, it should be condemned, and *per contra* if in a suspicious locality the bacteriological examination is bad the water ought to be condemned even though chemically it could be passed.—Muir and Ritchie.

The usually accepted standards for a surface water are:—

B. coli absent in 10 ml.

Streptococci absent in 10 ml.

B. Welchii absent in 100 ml.

Total colonies at 37° = 50 per ml.

„ „ „ 22° = 500 „

Wells, Ordinary or Medium Depth. *Total Bacteria.* The gelatin count may show from 100 to 2000 organisms per ml. The presence of *B. coli* in 10 ml. would condemn the water.

Wells, Deep. *Total Bacteria.* Should not exceed 100 bacteria per ml. Artesian wells and some springs may contain very small amounts, e.g., 5 or 10 organisms per 100 ml.

Presence of *B. coli* in 100 ml. or less cannot be permitted.

Rivers. Draw conclusions as under Wells (Shallow). Content varies enormously with season.

Total Bacteria. The gelatin count varies enormously. *B. coli* in 10 ml. would condemn.

Town Supplies (Filtered). *Total Bacteria.* Should not show more than 100 bacteria per ml.—Muir and Ritchie.

London (Lea River, filtered). Though *B. coli* in one series of examinations was present in 93% of samples in 1 ml. or less before filtering it was absent from 100 ml. in 62% of samples after filtering, and therefore present in 38% in 100 ml.—Sir A. C. Houston.

It has been stated that *B. coli* is to be expected in 100 ml. main tap water in London.

NOTES FROM THE METROPOLITAN WATER BOARD REPORTS

London Water is chiefly derived from two rivers which are undoubtedly polluted, less than 20% being obtained from the deep wells of Kent and the Lea Valley (17th Ann. Rep., 1923). The count of *B. coli* in the raw waters was found to be: Thames, 19 per ml.; Lea, 5 per ml.; and New River, 2 per ml.; and the total bacteria count in the same waters in 1912-13 amounted to 6,550, 11,772 and 2,777 per ml. respectively.—Sir A. C. Houston, *Brit. med. J.*, ii/1912, 1671; ii/1913, 679.

The water from 24 wells in Kent, supplying 27 million gallons, was exceeding pure, the bacterial count being 6 per ml. on gelatin and 0·05 on agar. *B. coli* was absent in 100 ml. in 94% of the samples. Chemically, the same water yielded ammonia 0·0002 and albuminoid ammonia 0·0026 parts per 100,000.—21st Ann. Rep., 1926.

Purification. The most efficient method developed was started at the Walton works in 1926 and consists in storage in reservoirs and double filtration followed by chlorination (see p. 486). The storage reservoirs constitute a chain of 49 lakes covering 2,700 acres, capable of storing 20,000 million gallons. After preliminary rapid filtration—100 to 200 gallons per hour—effects a notable saving by removing much of the material which tends to choke the slow sand filters so that the latter are able to work five times as fast and last longer.—17th, 19th, 20th, 21st Ann. Rep., 1922-26.

Raw waters are considerably altered in character by storage, with a tendency for the ammoniacal nitrogen, turbidity, and colour tests to show proportionately greater reductions than the albuminoid nitrogen and permanganate tests. Raw Thames water containing *B. coli* in 57·7% of the samples in 0·1 ml. or less showed, after storage at Chelsea, *B. coli* in 57·6% of the samples in 100 ml.—24th Ann. Rep., 1929.

Leptospira. The appearance of *Leptospira* in most filtered waters and even in that from deep wells, presents a new problem in water purification. Most cultures proved to be non-pathogenic and the organisms are very susceptible to minimal doses of chlorine.

Taste in Water. Fishy taste has been traced to *Endorina*, *Pandorina* and *Uroglena*; a cucumber-like taste to *Sycura*; an aromatic taste, to *Astirionella* and *Tabellariæ* (20th Ann. Rep., 1925). The leaves, twigs, etc., of willows, poplars and meadowsweet are capable of producing an iodoform-like taste on chlorination probably due to salicyl compounds.—24th Ann. Rep., 1929.

Anti-Bacterial Action of the Water of Certain French rivers. These have inhibitive or actual destructive effect on growth of intestinal bacteria, e.g. antagonistic action to *B. coli* of the Saône, to *B. typhosus* of the Rhône, to *paratyphosus A* of the Izère, and *B. dysenteriae Shiga* of the sea at Havre. May serve to explain why certain regions and persons are immune to water-borne diseases.—Brit. med. J. Epit., i/1926, 40.

Sewage (Crude). Total organisms in London sewage found to be 6 to 10 millions per ml. *B. coli* never fewer than 100,000 per ml.—Klein and Houston.

CHEMICAL AND BACTERIOLOGICAL EXAMINATION OF DRINKING WATERS COMPARED

A water may pass certain chemical standards and yet be unsatisfactory from the bacteriological aspect. The converse may also be true in some cases.

The following tables, prepared from results obtained by W. H. Martindale illustrate this point.

The waters comprise a selection as supplied from the main consumers in some of the leading cities and health resorts in Great Britain, including, e.g., London, Glasgow, Bath, Blackpool, Buxton, etc.

The results suggest that (1) Neither bacteriological nor chemical examination is adequate individually but together they constitute an adequate safeguard to the purity of water; (2) the absence of *B. coli* from 100 ml. of a water is an ideal seldom attained. (3) the albuminoid ammonia content is no indication of the number of bacteria, but in conjunction with chlorine, nitrite and nitrate, data may suggest sewage contamination; (4) examination of waters at the source and after traversing some miles of water supply pipe may show marked differences.

Source	Chemical				Bacteriological								Motility	Conclusions	
	Ammonia, parts per million		Chlorine parts per 100,000	Solids parts per 100,000 and effect on ignition	Bacteria per ml.		Vol. producing Acid and Gas in McConkey with		Rosindol Reaction	Indol Reaction	Fluorescence on Reibel-agar plates	Acid and Clot in Litmus Milk			
	Free	Alb.	Gelatin at 20°	Agar at 37° *	Glu-cose†	Lac-tose‡									Acid Clot
Water No. 1	Nil.	0.06	1	6 Much charred	100	160	ml. 10	ml. 10	+	+	+	+	+	Chem., good. Bact., not satisfactory.	
No. 2, Bath...	0.02	0.034	2	36 slight charring	972	8	100	100 50 acid only	—	—	—	+	+	Chem., excellent. Bact., satisfactory.	
No. 3 ...	Nil.	0.06	1.5	12 slight charring	1209	57	10	50	—	+	+	+	+	Chem., good. Bact., satisfactory.	
No. 4, Buxton	0.03	0.12	1	15 much charring	45	80	None with 100 ml.	None with 100 ml.	—	—	—	—	—	Chem., safe. Bact., excellent.	
No. 5 ...	0.026	0.056	5	45 v. sli. charring	172	199	10	10	+	+	+	+	+	Chem., good. Bact., <i>not</i> satisfactory.	

No. 6	Nil.	0·026	3	30 not charred	1109	37	50	50	—	—	+	+	—	—	Chem., excellent. Bact., satisfactory
No. 7	0·026	0·03	1	3 charred	at least 1000 some liquefng.	820	10	10	—	—	—	—	+	—	Chem., excellent. Bact., might be better.
No. 8	0·08	0·12	1·5	18 charred	at least 1000 some liquefng.	1600	50	50	—	—	—	—	—	—	Chem., safe or- ganically. Bact., might be better.
No. 9	0·01	0·036	6·5	45 v. sli. charring	1040	242	50	50	—	—	—	—	—	—	Chem., excellent. Bact., satisfac- tory.
No. 10, Village Well A		0·08	0·168	10·5	70 charred	10	60	1	10	+	+	+	+	+	+	Chem., unsatis- factory. Bact., bad.
Ditto B	...	0·026	0·12	10·5	68 charred	<i>B. sub- tilis</i> pre- vented count	75	100	100	+	—	+	+	+	+	Chem., unsatis- factory. Bact., satisfac- tory.
No. 11	...	Nil.	0·11	1·5	6 much charred	3000	50	10	10	+	+	+	+	+	+	Chem., safe or- ganically. Bact., unsatis- factory.
No. 12* London A ...		Nil.	0·04	1	32	less than 10 Nil.	20	100	ml. 100	+	—	+	+	+	+	{ Chem., excel- lent. Bact., satisfac- tory.
London B ...		Nil.	0·03	1	32		21	100	50	+	+	+	+	+	+	

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Source	Chemical				Bacteriological										Motility	Conclusions
	Ammonia. Parts per million		Chlorine parts per 100,000	Solids parts per 100,000, and effect on ignition	Bacteria per ml.		Vol. produc- ing Acid and Gas in Mc- Conkey with	Rosindol Reaction	Indol Reaction	Fluorescence on Rebipel- agar plates	Acid and Clot in Litmus Milk					
					Gelatin at 20°	Agar at 37° *					Glu- cose†	Lac- tose†	Acid	Clot		
	Free	Alb.														
No. 13	Nil.	0.08	2	21 slight charring	1400	1350	10	10	+	+	+	+	+	Chem., good. Bact., not satis- factory.		
No. 14, Margate	Nil.	0.04	2.5	30 not charred	800	30	10	10	—	—	—	—	—	Chem., excellent. Bact., satisfac- tory.		
No. 15, Nor- folk (Private well before repair)	0.026	0.076	4	40	52	32,000	1/100	1/100	+	+	+	+	+	Chem., org. safe. Bact., bad.		
Ditto (after repair)	0.1	0.07	4	36	70	157	10	50	—	—	—	—	—	Chem., org safe. Bact., improved, now safe, sub- ject supervision.		

* Pathogenic and intestinal organisms grow best at this temperature.

† Presumptive evidence of *B. coli*, *B. paratyphosus*, *B. enteritidis*, but excluding *B. typhosus* and dysentery organisms.

‡ Confirmatory for *B. coli* since *B. typhosus*, *B. paratyphosus*, *B. enteritidis* and dysentery organisms do not give it.

Columns 7 to 13 include the "Flaginac" reaction.

Columns 9, 10, and 14 show results of cultures in peptone water from least quantity of McConkey's Culture showing acid and gas.

CHLORINATION OF WATER.

A survey of the known methods of sterilisation of water shows that no method so economical or expeditious as chlorination exists.

Sir A. C. Houston first used an alkaline hypochlorite in 1905 at Lincoln in a typhoid epidemic. The method is in use in many parts. In Bogotá (Colombia) typhoid diminished on the introduction of the process. It is done either after or before filtration. In some cases a large excess of chlorine is added to destroy algae as well as bacteria, the excess being removed by means of SO_2 . Chlorine produced by electrolysis of sea-water is used in some parts instead of chlorine cylinders. In France, eau de Javelle is employed. In the Bunau-Varilla method in use at Rheims the amount of chlorine used is small and the good results do not seem capable of explanation on the basis of chemical interaction. (See T. H. Bishop, *Lancet*, i/1929, 371; also E. W. Wade, *J.R.A.M.C.* Oct., 1928).

Sir A. C. Houston (*Rep. metrop. Wat. Bd.*, 1930) states that "chlorination has come to stay." In 999 cases out of 1000 it is possible to produce a tasteless as well as a safe water supply. Probably the most effective method is the use of ammonia and chlorine in the proportions of 1 to 4 or 1 to 8, in a small volume of water which is then added to the water in bulk. The increased efficiency is due to the formation of a chloramine compound. The general trend of opinion appears to favour chlorination after filtration. Removal of any objectionable taste may be effected by the addition of potassium permanganate in doses of 0·2 to 0·8 parts per million, before, with, or after the chlorine treatment. Results obtained on New River Water (*Rep. metrop. Wat. Bd.*, 1931) illustrate results obtained by this treatment: of 238 samples, 62% showed *B. coli* in 1 ml. or less before chlorination and no *B. coli* in 71% of the samples after chlorination.

The enteric fever mortalities per 100,000 of Paris, London and Berlin for 1929 were 4·1, 1·0, and 0·9 respectively. Thanks to Philippe Bunau-Varilla and his advocacy of the chlorine process of water sterilisation, to which he has given the term "verdunisation," Paris in 1932 has at last achieved a reasonably safe supply of drinking water.—*Lancet*, ii/1932, 590.

Liquid chlorine has many advantages over the use of "Bleach"—the 100% purity of the sterilising agent, elimination of nearly all labour costs, and less likelihood of complaints as to taste, as it permits of more accurate dosage and better distribution of the chlorine in the water. In some cases the chlorine is dissolved in water through a pulsating meter before mixing; in other it enters the water through a diffusion plate of carborundum sponge.—J. Rice *Chlorination of Water*, 1918.

Nesfield found 0·125 g. chlorine per litre (125 per million) in water teeming with *B. typhosus*, *B. coli*, etc., sufficient to sterilise it in 5 minutes. One part per million acting for 15 minutes will kill cholera vibrio in it.—*Lancet*, ii/1910, 1213.

Sterilisation by means of chlorine in proportion of 1 in 500,000 with 3 minutes' contact. The gas made by acting on potassium chlorate with concentrated HCl —both of which have the advantage of keeping indefinitely in any climate.—J. J. Harper Nelson, *Brit. med. J.*, i/789, 815. *cf. also Calx Chlorinata Vol. I, p. 41.*

Chlorination may play a part in preventing the breeding activities of *Stegomyia fasciata* (*Aedes ægypti*), thus aiding the campaign against yellow fever. In countries bordering the Gulf of Mexico, where the water is filtered and chlorinated, yellow fever has been got under control, whereas on the West Coast of Africa, where this is not done to any extent, cases still occur.—Bunau-Varilla, per *Trans. R. Soc. trop. Med. Hyg.*, 1929, 395.

The "**Chlor-Sparklet**" apparatus enables the use of **Chloramine** (cf. Vol. I., p. 51, *et seq.*) to be applied in effective doses to small quantities of water by an unskilled person.

The apparatus involves the preparation of chlorine water from a chlorine capsule and then adding an ammoniacal solution made from tablets supplied.

Two chloramines exist:

Chloramine, which is rapid in action, but whose protection against reinfection disappears after 24 to 48 hours.

Dichloramine, which is slower in action (allowing 2 hours before using for drinking) but protects the water from reinfection for periods up to a week.

Chloramine is prepared by using two tablets to each syphon full, whereas with Dichloramine only *one* tablet is required.

Succinchlorimide suggested for war service in U.S.A. as acting promptly and being non-toxic. Bleaching powder said to be too erratic.—*Lancet*, i/1929, 352.

A plant was put down at Ottawa in which chloramine was used. Although slightly more expensive, it is stated to have the advantage of preventing after-growth, which is a serious problem on the continent. A tablet containing 6 mg. will disinfect about 25 fl. oz. of water in a few minutes, the only taste imparted to the water being that of chlorine.—C. R. Downs, *Industr. Engng Chem.*, 1934, 26, 20.

Further Methods of Sterilisation

The Excess Lime Method of treating water is effective for sterilising and purifying, and when necessary softening water.

The bactericidal dose is about 1 to 2 parts of CaO per 100,000 parts of water, the excess lime being removed by means of carbon dioxide. If the consumers of London water generally demanded a softened water, were prepared to pay for it, and Parliamentary sanction could be obtained, investigations have proved that the method is sound on chemical, bacteriological and physical grounds.—Sir A. C. Houston, *Rep. metrop. Wat. Bd.*, 1930.

The Southend Waterworks Company initiated the Excess Lime Method, in 1929 at Langford, to provide a supply of 7,000,000 gallons of purified and softened water per day, the raw water being both extremely hard and also contaminated. The results are excellent, no *B. coli* being found in 100 ml. of the treated water, the hardness averaging 10 parts per 100,000, albuminoid ammonia being reduced from 0.0245 to 0.0041 parts per 100,000 and the oxygen absorbed in 3 hours at 37° reduced from 0.235 to 0.060. A detailed description of the plant and method of operation.—*Municipal Review*, March, 1930, per *Rep. metrop. Wat. Bd.*, 1930.

Copper was suggested some years ago by H. Kraemer as a domestic measure for ridding water of *B. coli* and *B. typhosus*. His recommendation was to immerse a strip of copper foil in the water, e.g., a piece 3½ inches square being used in a quart of water for six hours.

Martindale conducted in 1929 a number of experiments on the possible bactericidal action of the metal used in this manner, but did not find the contention substantiated.

Cushny, referring no doubt to Kraemer's work, relates that certain organisms in water, stored in a copper vessel, are affected and killed by copper in solutions so dilute that the metal is not detected chemically.—J. Wilson Dougal, *Pharm. J.*, i/1928, 216.

Silver has been used, the action being due to solution of the metal (1 in 20,000) (Kling, *Brit. med. J. Epit.*, ii/1932, 14). The silver probably forms an association with the bactericidal protein (Leader, *Lancet*, i/1934, 93). Water may be rendered sterile and bactericidal by filtration through porcelain candles previously heated at 1200° after having silver chloride fused into their medium. The bactericidal effect is lost after 5 days.—Lakhovski, *C.R. Acad. Sci., Paris*, 1932, 194, 137.

The Catadyn Process is based upon the action of minute amounts of metal. The vessels consist of filtering devices with an active silver surface. 21 million germs per ml. of water killed in 48 hours. For special purposes and household use the method may have a considerable future but is too expensive for employment on a large scale.—Biggar and Griffiths, *Brit. med. J.*, ii/1932, 883; *Pharm. J.*, ii/1929, 87; *Rep. metrop. Wat. Bd.*, 1930.

Ozone has been utilised abroad, but is far more expensive than chlorine.

A large number of experiments were carried out on the ozone treatment of water, a plant, capable of dealing with 5120 gallons per hour, having been installed at Barn Elms (*Rep. metrop. Wat. Bd.*, 1931). Bacteriologically the results were perfect and the treatment improved the water chemically and physically. The treatment is more expensive than chlorination (0.260d. per 1000 gallons).

Ultra-violet Light. Bacteria in water can be killed with remarkable speed by ultra-violet rays. The Cooper Hewitt apparatus provides 132 gallons of sterile water per hour. With a flow of more than 600 cubic metres per 24 hours through the machine, and a consumption of less than 26 watts per cubic metre, content of 500 to 1000 *B. coli* per litre and total germs of 20 to 260 germs per cubic centimetre in the in-flow, the *B. coli* were reduced to nil and the "germs" to practically nil in the out-flow. It destroys both pathogenic and non-pathogenic organisms and all spores.

SWIMMING-BATH WATER

Chlorination of Swimming-Bath Water. The water is circulated by a pump, passing first through a gauze strainer. It is then treated with an aluminic ferric coagulant, to separate colouring matter and impurities, passed through closed pressure sand-filters, and aerated. Finally, it is treated with Cl₂, about 1 part per 2 millions, and returned to the bath heated. Analysis of water so treated after 19 weeks' use at the St. Helen's Public Baths showed 112 bacteria per ml. on gelatin in 3 days, *B. coli* and *B. enteritidis sporogenes* entirely absent in 100 ml.; nitrites and free chlorine were absent, and the free ammonia was 0.0046 and albuminoid ammonia 0.0058 per 100,000. It is claimed that the process enables the same water to be used for twelve months at a time. (Apparatus supplied by the Paterson Engineering Co., Ltd., London).—*Brit. med. J.*, ii/1925, 349.

Electrolysis of a mixture of sodium and magnesium chlorides in production of a stable disinfectant—used at Poplar. F. W. Alexander's preparation is hypochlorite relatively free from chlorate and rendered stable by a slight excess of the base. Used for swimming-baths. A difficult problem to clean the water effectually.—*Lancet*, i/1926, 357.

WATER STERILISATION FOR ARMY USE

Horrocks's Water Testing Method is used to determine the amount of bleaching powder required to sterilise the contents of an army water-cart.

The method uses zinc iodide, or potassium iodide and starch solution, as reagent.—Compare *Field Sanitation* by Moor and Cooper (Baillière, Tindall and Cox).

The test automatically adjusts the strength of the purifier to be used, to the particular water to be treated. The Horrocks's Test Case contains 6 white enamelled tumblers (170 ml.) and 1 black one (250 ml.). Bleaching powder—a levelled scoopful of about 2 g.—is rubbed fine and dissolved in the black tumbler filled to the inside mark. The white tumblers are filled with the water to be tested. One drop (1/15 ml.) of bleaching powder solution is added to No. 1, two drops to No. 2, up to 6 drops in No. 6. These are stirred and left for 20 minutes, when about 6 drops of a stock solution of potassium iodide and starch are added to each. A blue colour will indicate that after all organic matter has been destroyed an excess of available chlorine remains whereby iodine is liberated, with the formation of the blue iodide of starch. The number of the first tumbler of the series which shows a definite colour, gives the number of scoops of the bleaching powder required to sterilise the contents of one water-cart (110 gallons approx.). The powder should be dissolved before adding it to the water-cart and contact for one hour should be allowed, before the water is issued to the troops.

Alum Box, in the army water-filtering cart, contains a mixture of alum 75% and dry sodium carbonate 25%. By the action of the water, aluminium hydroxide is formed and deposited on the filter cloth, the jelly-like mass formed imitating the natural zoogloea layer of a sand filter-bed.

POISONED WATER

A set of tests for examination of **wells for troops on the march**, including examination for **cyanides, alkaloids**, e.g., strychnine (using bismuth potassium iodide and phosphomolybdic acid), **arsenic** (using zinc, HCl and mercuric chloride spot on filter paper), **mercury** (using copper foil and HCl), and **copper** salts (using hæmatoxylin solution, which turns a deep blue with copper and iron salts). Distinguish copper from iron by adding a few drops of HCl and then a few drops of freshly made potassium ferrocyanide solution. If the precipitate be maroon-coloured no iron but much copper is present. If both copper and iron be present the maroon precipitate of copper will be obscured. In this case insert the polished blade of a pocket-knife in the water with a few drops of HCl, and note deposit. The water, if necessary, may be concentrated.—John Parry, Kimberley. *Chem. and Drugg.*, ii/1915, 554.

The **Army Sanitary Committee** gave the following scheme for detecting Poisons:—

(1) **Biological Test.** If possible note effect on fish.

(2) **Chemical Tests.** Add sodium sulphide solution, *q.s.* Brown colour indicates probable presence of a metal (but the absence of a colour does not indicate absence of arsenic).

Add hydrochloric acid, *q.s.*—

(a) If the colour remains black or brown, **lead, copper or mercury** is present.

(b) If canary-yellow forms, **arsenic** is present. (Ignore slight milkiness of sulphur).

Confirm by conducting a "Marsh" with a small test-tube and glass jet, allowing the lit hydrogen flame to impinge on a porcelain plate. Black stain insoluble in dilute hydrochloric acid indicates arsenic or antimony.

For **cyanide**. Add caustic soda solution and a few drops of ferrous sulphate solution. Boil thoroughly. Add hydrochloric acid, *q.s.* Blue colour indicates cyanide, especially on standing for 30 minutes.

MINERAL WATERS

The following information regarding mineral waters has been obtained by applying in most instances direct at the sources.

The arrangement of the paragraphs is as follows:—

The name of the water and locality is given, then follow in order the names of spring or springs, the nature of the water, the chief chemical constituents, the medicinal uses, the season, if any, at the health resort, and an indication as to whether the water is imported in the bottled condition. The accounts of some are, however, condensed. "Sulphurous" is to convey hydrogen sulphide with (usually sodium) sulphates and sulphides.

***Trade Marks.** A search has been made in Classes III and XLIV of the Register for the purpose of this chapter.

Aedipsos (GRECIAN).—Saline, thermal. **Aegina** (GRECIAN).—Alkaline. Imported.—Ph. Notes.

***Aesculap.** T.M. 22666, Class 44; 185183, Class 3. (HUNGARY).—Magnesium and sodium sulphates, sodium chloride and calcium sulphate. Occasional and habitual constipation, bowel and liver disorders. Imported.

Aix-lex-Bains (SAVOY, FRANCE).—Sulphur and an organic matter called barègine, which renders it easy of digestion, oily and suitable for massage. Rheumatism, gout and throat diseases. 1st April to end of October. Also imported. Employed as tubs, shower bath, massage and vapour baths.—L. Blanc, *Lancet*, ii/1915, 174.

The distinctive feature of the Aix thermal treatment is the douche-massage known throughout the world as the Aix douche; the patient has streams of water directed on him while seated in a chair.—*Brit. med. J.*, ii/1921, 118. See also Preston King, *Brit. med. J.*, ii/1925, 635.

Alet (AUDE, FRANCE).—Source des Bains and Source Nouvelle.—Alkaline carbonated. Debility, dyspepsia, anæmia. Imported.

Allevard (ISERE, FRANCE).—Sulphurous carbonated. Calcium and magnesium bicarbonates, sodium chloride, calcium, sodium and magnesium sulphates, free hydrogen sulphide, carbon dioxide and nitrogen. Chest affection of all kinds, skin diseases, women's diseases, rheumatic complaints. June 1st to September 30th, and imported.

***Apenta** (BUDAPEST, HUNGARY).—Saline aperient. Magnesium, sodium and calcium sulphates, sodium, magnesium, calcium bicarbonates and sodium chloride. Hæmorrhoids, chronic affections of the respiratory and circulatory organs, gouty disorders.

***Apollinaris**. T.M. 153705 and 283030, Class 44. (NEUENAU, GERMANY).—Acidulated alkaline table water. Sodium chloride, calcium and magnesium bicarbonates, with large excess of carbon dioxide. Catarrhal affections of the respiratory organs and mucous membrane, acute and chronic laryngitis, bronchitis, dyspepsia, gout and gravel. Imported.

***Aquaperia**. T.M. 363617, Class 44. (HARROGATE, GT. BRITAIN).—A natural tonic aperient water, standardised and of high organic purity. Dose: a wineglassful before breakfast. For constipation, liver disorders and biliary complaints. Relieves gout and rheumatism and helps to prevent indigestion.

Aix-les-Thermes (PYRENEES, FRANCE).—Altitude 2000 ft. Alkaline sulphur from a number of springs. Radioactive, organic matter termed *barégine*. Gout and rheumatism, respiratory troubles and skin affections.—*Lancet*, ii/1922, 826.

The ground is warm with hot springs and the snow melts in consequence. Some of the springs are milky with colloidal sulphur. In other springs the alkalinity, due to sodium carbonate and silicate and some lithia is pronounced. Professor C. Moureu has shown that the gas evolved from the Source Viguerie at Aix contains argon and helium, as well as nitrogen. The composition of the gas was found to be:—Nitrogen 98·45%, argon (with traces of krypton and xenon) 1·453%, helium (with traces of neon) 0·097%. The presence of the inert gases points to a radioactive origin, to which may be due the beneficial results from the treatment with the thermal waters. The curative properties have been known for a long time.—J. G. F. Druce, *Chem. & Drugg.*, i/1927, 323.

Bagnères-de-Louchon and Bagnères de Bigorre (WESTERN PYRENEES, FRANCE).—Alkaline sulphurous. Sodium sulphide and hydrogen sulphide. Gout, chronic rheumatism, respiratory and cutaneous troubles. Mid-May to mid-October.—*Lancet*, ii/1922, 880.

Bagnoles-de-l'Orne (NORMANDY, FRANCE) Grande Source.—Small quantities of sodium chloride, sodium sulphate and silica, also traces of potassium, iron and calcium salts. Used chiefly as baths and douches but is also drunk. Phlebitis, varicocele, women's diseases and rheumatism. May 15th to October 1st; imported.

Barèges (HAUTES-PYRENEES, FRANCE).—Sulphurous, warm. Sodium sulphhydrate and sulphate, sodium chloride, silica. Chronic rheumatism, skin and bone diseases. Imported.

Barium (LLANGAMMARCH WELLS, WALES).—Saline. A tumbler full three or four times daily. Sodium, calcium, magnesium and barium chlorides. Gout organically. Only 0·0056 gr. per gallon of albuminoid ammonia. Contains no sulphates owing to presence of barium. Heart affections, glandular swellings, skin affections, rheumatism. Bottled, both aerated and still.

Bath. The only thermal spring in England, and one of the oldest in Europe. King's Bath Spring.—Calcium sulphate 102·88 gr., sodium sulphate 23·5 gr., magnesium chloride 15·8 gr., per gallon, and other salts in less proportion. Radium has been found in the waters and deposits, also argon, helium, krypton and xenon.

King's Well contains 0·1387 mg. of radium per million litres. If the niton (emanation) were represented by the weight of radium capable of forming the niton present in a million litres of water or gas, the figures for the water of the King's Well, Cross Bath and Hetling Bath are respectively 1·73, 1·19, and 1·7 and for the gas from the King's Well 33·65. The gas from the King's Well contains about four times as much niton as is contained in the natural gas from Buxton, viz., 7·7 and 8·5 mg. per million litres. Further data Vol. II, XVIIIth Edn., p. 457. (See also SULIS, i.e., bath water aerated and bottled.)

Ben Rhydding. See **Ilkley**.

Besançon (JURA).—Saline springs with bromides and iodides. Children's diseases and gynæcological conditions, e.g., sterility.—*Lancet*, i/1924, 1037.

★**Bethesda**. T.M. 171394. (WISCONSIN, U.S.A.)—Alkaline, calcium and magnesium bicarbonates. Kidney diseases, Bright's disease, diabetes, torpid liver, dyspepsia, insomnia. Imported.

Bilin (BOHEMIA).—Alkaline acidulated table water, sodium carbonate, sodium chloride, sodium sulphate, lithium carbonate, free carbon dioxide. Catarrh of the stomach and of the respiratory organs, rheumatism and Bright's disease. Pastilles are also prepared.

Birmenstorf (SWITZERLAND).—Saline aperient. Constipation, jaundice hæmorrhoids, uric acid. Imported.

Bonnes (see EAUX BONNES).

Bourboule, La (PUY DE DOME, FRANCE), Choussy-Perriere Spring. Arsenated, 1 litre = 0.028 g. of crystalline sodium arsenate (1.9 gr. per gallon), sodium chloride and bicarbonate. *Dose*, a large tumberful. Debility, anæmia, chest affections, arthritis and diabetes. Imported.

Bourbon-Lancy (FRANCE). Oxygen is, in the majority of cases, absent in the gas of mineral waters, or present only in traces, but the gas of this spring contains 0.53%.—Prof. C. Moureu, *Chem. & Drugg.*, i/1923, 869.

Braceborough (LINCOLNSHIRE, ENGLAND).—Known since the reign of George III. The spring gives 200,000 gallons a day at 50°F. Calcium bicarbonate 30, calcium sulphate 6.6, magnesium sulphate 2.26 grains per gallon. Free CO₂, 2.1 grains per gallon. Bottled. *Dose*.—One to two tumblerfuls first thing in the morning and at night. In psoriasis, erysipelas, eczema, and other skin affections; also in nervous conditions.

Successful in gout. Relieved excessive micturition. Digestion improved.—A. Eddowes, *J. clin. Res.*, April, 1925.

Brides-les-Bains (SAVOY, FRANCE).—Alkaline saline. Contains sulphates of sodium, magnesium and calcium, and chloride of sodium. Obesity, uric acid, hepatic complaints, gastro-intestinal diseases, constipation. Imported. Description of resort and water. Closely analogous to the Sprudel Source at Carlsbad.—*Brit. med. J.*, i/1920, 545. See also *Lancet*, i/1924, 1037.

Brucourt (CALVADOS, FRANCE).—"Star" Spring.—Chalybeate. Tonic in anæmia. Imported.

Buffalo Lithia (MECKLENBURG CO., VA., U.S.A.).—(No. 2 the chief spring). Alkaline lithiated table water. Albuminuria, uric acid diathesis, and other affections needing alkaline treatment. June 15th to October 1st, and imported.

Bussang (VOSGES, FRANCE).—Ferruginous tonic and digestive. Free carbon dioxide, sodium, calcium, magnesium, bicarbonates with manganese, iron and arsenic. Anæmia, chlorosis, jaundice, gout, rheumatism, diseases of women. June 15th to September 15th, and imported.

Buxton (DERBYSHIRE).—Slightly saline. Sodium chloride, magnesium carbonate, calcium carbonate, free nitrogen and carbon dioxide. Stomach, bladder, liver, and kidney disorders, skin affections, gout, rheumatism, sciatica. All the year round and bottled.

The gentlemen's Natural Baths contain 1.1 mg. per million litres of niton, i.e., about the same as the Cross Baths at Bath.—Sir Wm. Ramsay, *Brit. med. J.*, i/1912, 617; *Lancet*, ii/1912, 746; *Pharm. J.*, i/1912, 373.

Valuable in alleviating chronic articular gout and rheumatism—irregular forms of gout are benefited and acute attacks cut short. The mineral constituents only amount to 27 grains per gallon, chiefly carbonates of calcium and magnesium, sodium chloride with traces of iron and manganese. The gases contained show a unique richness in nitrogen.

Buxton Mineral Water. As a result of experiments the following conclusions have been drawn: (1) It has a diuretic effect superior to distilled water. (2) It increases the elimination of sodium chloride. (3) It increases hydrion concentration and favourably influences metabolism.—*Lancet*, ii/1923, 1301.

Buxton Water has a stimulant effect on nitrogen metabolism and produces conditions favourable for more complete oxidation.—*Brit. med. J.*, i/1924, 17.

MINERAL WATERS AS DIURETICS. The aim of their employment in diuresis is to promote the excretion of harmful solids, rather than the mere excretion of water, and for this purpose mineral waters of low concentration have been found superior to distilled water. The total amount of salts in a dose of mineral water which would produce diuresis is very much less than that required in an artificial

solution. Three types of mineral waters possess diuretic properties—sulphur water, including the sulphuretted salines, the calcareous, and the radio-active thermal waters of low mineralisation.—C. W. Buckley, *Lancet*, ii/1923, 1300.

★ **Cachat.** T.M. 293559 and 293558, Class 44 (*see* EVIAN, Source Cachat).

Capvern (HAUTES PYRENEES, FRANCE).—2 springs; Houn-Caoude (drinking) and Bouridé (baths). Alkaline. Catarrh of bladder, gravel, gall stones, women's diseases. May to October. Imported.

Carabana (SPAIN).—Purgative. Sodium sulphate. Intestinal and hepatic affections and dyspepsia. Imported.

Cauterets (PYRENEES, FRANCE).—Sulphurous. Hydrogen sulphide, iodine. Skin and lung diseases, glandular swellings. Summer and imported.

The gas given off at the spring by this mineral water consists of 98·55% nitrogen.—Prof. C. Moureu, *Chem. & Drugg.*, i/1923, 869.

Cerigo (GRECIAN).—Chalybeate. Imported.—Ph. Notes.

Challes (SAVOY, FRANCE).—Sulphurous. Chronic catarrh, skin affections and intestinal diseases. May to October. Imported.

Chateldon (PUY DE DOME, FRANCE).—Alkaline acidulated. Stomach and urinary disorders, anæmia, and as a table water. Imported.

Chatel Guyon (AUVERGNE, FRANCE).—Source Gubler. Alkaline. Dyspepsia, jaundice, anæmia, constipation, uric acid. May to October. Imported.

Cheltenham (GLOUCESTERSHIRE).—Pittville Waters: No. 1 Cheltenham, alkaline, sodium chloride, sulphate and bicarbonate; No. 2, less sodium chloride, more sulphate; No. 3, more sodium sulphate but less than No. 2; No. 4, **Cheltenham "Magnesia,"** magnesium sulphate 117 grains per gallon and sodium sulphate; No. 5 is No. 4 concentrated. No. 6 is Cheltenham sodium sulphate saline, sodium sulphate in predominance. *See also Pharm. J.*, ii/1915, 571.

Claudia (SORGENTE DI ANGUILLARA, SABAZIA, near ROME).—Alkaline. Carbon dioxide with small quantities of alkaline bicarbonates. Gastric dyspepsia. Imported.

Condal (RUBINAT, LERIDA, SPAIN).—Aperient. Sodium, magnesium, calcium and potassium sulphates, sodium chloride. As a purgative for habitual constipation, plethora, etc. Imported.

Condillac (FRANCE).—Alkaline acidulated table water. Imported.

Contrexéville (VOSGES, FRANCE).—Pavillon Spring. Alkaline, anti-rheumatic. Gouty affections, dyspepsia, eczema, catarrh of the bladder and liver. May 20th to September 20th, and imported. Contrexéville Source Mignon is also supplied.

Why does Contrexéville water, containing much calcium, cure or alleviate gout? Probably it is not so much the calcium content of the water as its influence on metabolism.—F. E. Tylecote, *Med. Pr.*, 1929, 261.

Coulsworthy (NORTH DEVON).—Alkaline. Detergent, osmotic and diuretic.

Dax (called locally La Néhe).—Thermal—has temperature 61°C. Owing to evolution of nitrogen it appears to be boiling. Contains sulphates and chlorides of calcium and sodium. The mud contains a large proportion of living algæ—the *Oscillaria calida*. Is distinctly radio-active. In rheumatism.

Desaignes (Eau de César) (ARDECHE, FRANCE).—Alkaline acidulated table water. Imported.

Dolecoed. *See* Llanwrtyd.

D'Orezza (CORSICA). Chalybeate table water. Anæmia, dyspepsia; useful after prolonged illness, or for weakness. July 1st to September 1st. Imported.

Droitwich. *See* ★ Wychia.

Eaux Bonnes (BASSES PYRENEES, FRANCE).—Mild sulphurous. Helium is given off by the water—due in all probability to radium-containing mineral at the source. Similar to Barèges and Cauterets. Bronchial catarrh, phthisis, neurasthenia, asthma. June 1st to October 1st. Imported.

Has reputation of curing sterility in women.

Enghein-les-Bains (near PARIS).—Sulphurous. Lung and skin affections, uterine disorders, nervous diseases, nose and ear affections. May 1st to October 15th. Imported.

Epidaurus (GRECIAN).—Imported.—Ph. Notes.

★ **Esvach.** T.M. 224276.—Aperient. Magnesium, sodium and potassium sulphates and bicarbonates, free carbon dioxide. Habitual constipation, indigestion, biliousness, gout. Bottled.

Evian-les-Bains (HAUTE SAVOY, FRANCE) Sources "Cachat" and La Croix.—Alkaline table water. Calcium and magnesium bicarbonates, free carbon dioxide. Liver and intestinal disorders. For washing out bladder in uric acid troubles; calculi, cystitis. May to October.

Fango Mud Springs (ITALY).—Installation at Matlock. For the treatment of rheumatism.

Farris (NORSKE MINERALKILDER, LARVIK, NORWAY).—Mineral table water. Radio-active; gout and rheumatic complaints.

Fayet St. Gervais (SAVOY, FRANCE).—Saline and sulphur springs, for arthritic troubles, skin diseases, rhino-pharyngitis and neurasthenic conditions.—*Lancet*, i/1924, 1037.

Fiuggi (ITALY).—Saline. Sodium chloride, potassium nitrate, calcium carbonate, carbon dioxide, ozone, and oxygen (possibly due to action of radium emanations contained), nitrogen. Gastric complaints. Imported. Full report on.—*Lancet*, ii/1907, 915.

Flitwick (near AMPTHILL, BEDFORDSHIRE).—Ferruginous. Ferric persulphate and sodium sulphate. Anæmia, chlorosis, dyspepsia, general debility and neuralgia. Bottled.

Folkestone (KENT).—Contains about $2\frac{1}{2}$ to 3 grains of chalk per pint—if boiled, about $\frac{1}{2}$ grain—which cannot be considered deleterious or have any bad effect. Folkestone water is exceedingly pure, containing a trace only of free ammonia and 0.0008 grain per gallon of albuminoid ammonia. Total hardness 18.7, permanent hardness 2.9 grains per gallon.

★**Fontalis**. T.M. 242666 and 251903, Class 44.—A pure table water. Alkaline. Chlorides and carbonates, free from calcium and magnesium salts. Bottled at Harrogate.

Forges (NORMANDY, FRANCE).—Chalybeate. Ferrous bicarbonate. Chlorosis, dyspepsia. June 1st to October 1st. Imported.

Gilgit (KASHMIR, INDIA).—Goitre does not occur among the coolies who drink the pure water of the Gilgit river. Total solids 7 grains per gallon. Total hardness 4, calcium about 6, free ammonia and organic matter nil.—*Lancet*, ii/1906, 1570.

Grassion (FRANCE).—Bituminous. Throat and chest affections, gastric and vesical catarrh. Imported.

Gytje.—A kind of mud from the Norway fjords used in the "Gytje" treatment in balneology for gout and rheumatism.—Ph. Notes.

Harrogate (YORKSHIRE).—Sulphurous. Skin and rheumatic affections, e.g., eczema, psoriasis, lupus erythematosus, furunculosis, urticaria; also in anæmia, and dyspepsia. Aperient and diuretic. Summer and winter, and bottled. The sulphur and alkaline carbonates compose half the solid ingredients. The Beck-with Spring contains large proportion of magnesium. Helium has been traced in the gases rising, hence presence of radium is assumed. Hydrogen sulphide content has been stated as 10.46 cubic inches per gallon.

Some pharmacological effects of the strong sulphur water.—D. Brown, *Brit. med. J.*, i/1911, 1304.

Description of the spa.—*Brit. med. J.*, ii/1919, 78.

Barium in Harrogate waters. Stimulant action on muscular tissue. Barium content: "Old Sulphur" Spring 6.91, "Chloride of Iron" Spring 3.51, "Magnesia" Spring 3.97, per 100,000.—A. Woodmansey, *Lancet*, i/1923, 22.

"**Harrogate Salts**."—Potassium tartrate 360 grains, magnesium sulphate 1 lb., sulphurated potash 1 oz.—*Pharm. J.*, i/1907, 548.

Hathorn (see SARATOGA).

"**Hygyn**."—A natural alkaline spring water from Rickmansworth, Hertfordshire, containing a small amount of added sodium hyposulphite. Suggested for cases of "blood pressure" and as an internal antiseptic.

Hypate (GRECIAN).—Sulphurous. Imported.—Ph. Notes.

Igmandi (KOMAROM, HUNGARY) Water.—Radio-active. Saline aperient. Magnesium sulphate 29.3%, sodium sulphate 9.5%, calcium sulphate 0.7%, sodium chloride 0.8%. Total solids 40.8 per 1,000 g. Radio-activity inherent in the calcium sulphate.—*Lancet*, ii/1905, 777. Corpulency, constipation, hæmorrhoids, rheumatism.

Ilkley and Ben Rhydding (ILKLEY in WHARFEDALE).—Chalybeate and antacid. (i) Chalybeate Spring. Ferrous carbonate, calcium sulphate, and alkaline chloride. (ii) "Hygeia" Spring. Calcium, sodium, and magnesium carbonates, sodium sulphate. (iii) "Ilkley Wells." Gout and rheumatism.

Ilkley Wells (Old White Wells).—The composition from the content of acids and bases would appear to be ferric oxide 0·0159, calcium carbonate 0·8078, calcium nitrate 0·014, calcium silicate 2·0535, calcium sulphate 0·5199, magnesium carbonate 1·4235, magnesium sulphate 1·09, potassium carbonate 0·1548, sodium carbonate 0·8726, sodium chloride 1·155, lithium chloride 0·0831 grains per gallon.—B. A. Burrell, Yorkshire Geolog. Soc., 1914. *See also* HEALTH RESORTS.

Insalus (SPAIN).—Alkaline, carbonated. Affections of the stomach, urinary passage, kidneys and bladder.

Kyllini (GRECIAN).—Sulphurous. Imported.—Ph. Notes.

Kythnos (GRECIAN).—Saline, thermal. Imported.—Ph. Notes.

Labassère (HAUTES PYRENEES, FRANCE).—*See* Bagnères de Bigorre.

La Preste (EASTERN PYRENEES, FRANCE, about 50 miles from Perpignan).—In affections of the urinary tract—cystitis, vesical catarrh, prostatitis, etc. Contains only 11·2 grains per gallon total solids. Silica one of the leading constituents.

Latraki (GRECIAN).—Alkaline.—Ph. Notes.

Leamington (WARWICKSHIRE).—Saline. Calcium, magnesium, strontium and barium sulphates, sodium, calcium, magnesium and potassium chlorides, magnesium bromide and iodide, calcium and iron carbonates with traces of manganese and titanium. Dyspepsia, gout, women's diseases, sciatica, glandular swellings and skin diseases. Bottled.

★ **Levico** (AUSTRIAN TYROL).—Two springs (strong and mild); arsenical, chalybeate. STRONG: Arsenious acid, 0·99 part per 10,000—1/12th of a grain per pint; the MILD is 1/10th of this. Further constituents: Ferrous sulphate and ferric persulphate. Anæmia, skin eruptions, neuralgia and amenorrhœa.

Llandrindod (WALES).—"Strong Sulphur," "Roman Spring," "Magnesium Spring." The first is radio-active. In skin affections, dyspepsia, glandular enlargements, gout, rheumatism. Season, all the year round.

The hydrogen sulphide waters are of several strengths. One contains a small amount of thallium chloride and a considerable quantity of lithia—latter higher than Royat.—*Brit. med. J.*, i/1909, 1245.

Llangammarch.—*See* Barium.

Llanwrtyd, Dolecoed Spa (WALES).—Hydrogen sulphide, the strongest in Great Britain.

Loueche (Leuk or Loeche les Bains) (VALAIS, SWITZERLAND).—Warm, almost exclusively for baths. Calcium sulphate and magnesium sulphate, similar to that of Bath in England. Rheumatism, gout, women's diseases, skin affections. May 1st to October 15th.

Magnaris.—A table water prepared at Llandrindod.

Malvern (WORCESTERSHIRE).—Practically free from saline matter. Total $\frac{3}{4}$ grain per gallon only, and contains no organic matter. Bladder and kidney diseases and skin affections. Bottled.

★ **Malvern Selzer**. T.M. 4744 and 5.—Slightly saline table water.

★ **Malvernian**. T.M. 52502 and 86755, Class 44 (St. Anne's Spring, Malvern). A sparkling water, very saline, containing calcium carbonate 3, magnesium carbonate 2, sodium chloride 10, and sodium sulphate $\frac{1}{4}$ grain to the pint, together with a trace of silica. Bottled.—*Lancet*, i/1926, 350.

Marcols (ARDECHE, FRANCE), Source du Lion.—Alkaline table water. Stomach, liver and kidney diseases, rheumatism. Imported.

Martigny (VOSGES, FRANCE).—Lithiated. Gravel, diabetes, liver and kidney complaints.

Methana (GRECIAN).—Sulphurous.—Ph. Notes. So powerful as to render the place objectionable: the sea into which the water falls is milky, owing to the decomposition of the hydrogen sulphide. The bacterium *Beggiatoa nivea* is found in the sediment, and in the protoplasm of this organism particles of sulphur are distinctly visible under the microscope. Imported.

Miers (LOT, FRANCE).—Saline, laxative. Sodium sulphate, calcium sulphate, magnesium chloride. Dyspepsia, calculi, migraine, obesity, albuminuria. Imported.

Missisquoi (VERMONT, U.S.A.).—Sulphurous. Scrofula and other skin affections, diseases of respiratory organs. Imported.

Mont Dore (PUY DE DOME, FRANCE).—Alkaline, saline. Bicarbonates, ferrous carbonate, arsenic, and silica. Intestinal disorders, rheumatism, asthma, bronchitis and laryngitis. June 1st to September 20th. Imported.

Montmirail (FRANCE).—Sodio-sulphated. Mild aperient.

Montreux (SWITZERLAND).—Alkaline table water. Slightly mineralised. Stomach, liver, kidney and bladder affections. Imported.

Nocera Umbria (Angelica Spring, 185 kilometres from ROME).—Alkaline. Bicarbonates. Digestive, anturic, tonic, refreshing. Imported.

Orezza.—See **D'Orezza**.

★ **Osmos**. T.M. 386477.—Magnesium sulphate (anhydrous) 1·73%, sodium sulphate (anhydrous) 1·79%, sodium chloride 0·16%, sodium bicarbonate 0·18%. potassium and calcium salts—traces. Equivalent to Hunyadi Water.—*Brit. med. J.*, ii/1919, 346. Used for constipation, dyspepsia, obesity, hæmorrhoids, liver and kidney disorders.

Ostend (BELGIUM).—In the Parc Léopold is an artesian well yielding a radioactive water, practically free from lime and rich in boron (0·1494 g. sodium biborate per litre) hence unique in this respect; containing also sulphates, small amounts of iodine, bromine and arsenic together with dissolved gases: nitrogen 17·95 ml. per litre, argon 0·388, helium and neon 0·0194 and hydrogen sulphide 3·257 ml. per litre. Internally or as baths in arthritis, obesity, diabetes, gastrointestinal and genito-urinary affections, anæmia, skin and mucous membrane affections, pharyngitis and laryngitis. Contraindicated in tuberculosis and rachitis.—*Pharm. J.*, i/1925, 609.

★ **Perrier**. T.M. 287950 and 1. (VERGESE, nr. NISMES, FRANCE).—Slightly mineralised, organically pure. Small proportion of alkaline carbonates. Digestive.—*Med. Pr.*, June 22, 1904.

Pistany (previously called Postyen. A few miles from Vienna). Thermal mud baths, in rheumatic affections. For cases of sciatica and chronic periostitis, also internal catarrhs.—*Brit. med. J.*, i/1920, 545. Imported.

Plombières (VOSGES, FRANCE).—Mild saline. Sodium sulphate, arsenic, oxygen, nitrogen. Neurasthenia, gastralgia, dyspepsia, dilatation of the stomach and chronic diarrhœa, rheumatism, skin affections. May to September. Imported. Mucous colitis is treated by washing out the colon with the alkaline sulphur water and further bath treatment.

The gas given off at the spring by this mineral water contains 1·64% argon, with traces of krypton and xenon.—Prof. C. Moureu, *Chem. & Drugg.*, i/1923, 869.

Poland (U.S.A.).—Potassium sulphate, sodium, calcium and magnesium carbonates. In dyspepsia. Imported.

Postyen, see **Pistany**.

Pougues (FRANCE).—St. Leger Spring.—Alkaline. Dyspepsia, anæmia, scrofula, gravel, catarrh of the bladder. May 15th to September 30th. Imported.

★ **Presta**. T.M. 267852, Class 44. Raised by artesian boring (300 ft. deep) at Colindale, Hendon, N.W. London. It is therefore filtered through the natural chalk of the Chilterns on one side and the North Downs on the other. Bottled and used in making cordial waters—lemonade, ginger beer and ale, lemon squash, etc.

Pyrmont (WALDECK, WESTPHALIA).—Three springs. HAUPTQUELLE contains most iron.—Chalybeate. Chronic catarrh, digestive and urinary diseases, women's diseases, scrofula, rheumatism and gout.

Quicherat (FRANCE).—Ferruginous. Magnesium and sodium chlorides, with some iron and manganese, carbon dioxide. Anæmia, stomach diseases. Imported.

“**Radium Water**.”—From springs at Chao da Pena. Invigorating—advocated for rheumatism, sluggishness of gland action, faults of skin and hair, obesity, deterioration of nerves and arteries. Imported.

Ragaz-Pfäfers (CANTON ST. GALL, SWITZERLAND).—Thermal spring 99°F. Calcium, magnesium, and sodium chlorides, bicarbonates, and sulphates. Very free from bacteria. Rheumatism, gout, sciatica, neuralgia. General season May to October, but a Spring season begins middle of March. The waters belong to the simple thermal group. Description.—*Brit. med. J.*, ii/1921, 327.

Recoaro (VENETIA, LOMBARDY, ITALY).—Sources: Lelia, Lorgnia and Giuliana.—Ferruginous table waters. Sulphates. Intestinal and liver complaints. Tonic, easily assimilated. Summer and imported. ROYAL BITTER SOURCE.—Is pure bacteriologically. Purgative for intestinal complaints.

Rennine (REIPERTSWEILER, ALSACE).—Nitrated. Potassium nitrate 0·19 g. per litre, alkaline chlorides. Diuretic, laxative, in heart disease.

Renaion (FRANCE).—Alkaline, acidulated table water. Bicarbonates, free carbon dioxide. Dyspepsia and gastric disorders. Imported.

Roncegno (VALSUGANA, SOUTHERN TYROL).—Each litre contains 0·109 g. sodium arsenate, 0·115 g. arsenic anhydride, 0·03 g. ferric phosphate, 3·12 g. ferric sulphate, also sulphates of copper, magnesium, nickel and cobalt.—From information provided by the local authorities.

Has the highest content of arsenic in any spring, viz., 42·6 mg. As_2O_3 per litre.—*Pharm. J.*, i/1912, 689.

In addition to 0·007% As_2O_5 , O. Bennett found 0·004% antimony oxide.—*Pharm. J.*, ii/1912, 286.

Royat (PUY-DE-DOME, FRANCE).—Three springs. Saline, arsenated (small quantity), lithiated. Rheumatism, dyspepsia, nervous diseases, women's diseases, anæmia, skin affections and debility. Summer. Imported. Full description of this water.—*Brit. med. J.*, i/1907, 758.

Rubinat (PYRENEES, SPAIN).—"Llorach" Spring. Aperient. Rich in sodium sulphate 9·62%, and magnesium sulphate 0·32%, and contains calcium chloride. Stomachic disorders, constipation, liver and kidney affections. Imported.

Rubinat (SERRE, FRANCE).—Similar to the last-mentioned, but stronger than the above in the proportion of sodium sulphate to magnesium sulphate. Uses similar to the above. Imported.

Saint Boès (BASSES-PYRENEES, FRANCE).—Bituminous, iodised and arseniated. Arsenic, iodine. Skin, lung and venereal diseases. Imported.

Saint Galmier (LOIRE, FRANCE).—"Badoit" table water. Dyspepsia, intestinal catarrh, constipation, nervous disorders, hyperæmia. Imported. "Noel"—Alkaline. Acidulated. Uses as latter. Imported.

Saint Gervais (HAUTE SAVOIE, FRANCE).—Saline. Sodium and calcium sulphates, sodium chloride. Skin affections, constipation, rheumatism and nerve diseases. May 15th to September 30th. Imported.

Saint Moritz (SWITZERLAND). "Paracelse" Spring.—Alkaline, Chalybeate, tonic. Nervous and intestinal disorders, sick headache, hysteria, Graves' disease and for convalescence. All the year round. Imported.

Saint Sauveur—See **Vernet les Bains**.

Salies de Béarn (FRANCE).—Saline. Sodium bromide and iodide. Skin affections and as a general tonic.

Salins les Bains (JURA, FRANCE).—Tonic. Magnesium chloride, iodides and bromides. Anæmia, tuberculosis, general debility, women's diseases, obesity, and scrofulous affections. Summer. Imported.

Salins Moutiers (SAVOY, FRANCE).—The French rival of Nauheim and Kissingen; chloride of sodium, carbonate of iron, sodium arsenate, carbon dioxide, and radio-active substances. Peculiarly adapted, together with Brides-les-Bains, for Anglo-Indians.—*Lancet*, i/1924, 1037.

Sallyco.—Artificial. Is stated to contain colchicine and salicylic acid.

★**Salutaris**. T.M. 151567, 308459 and 312724, Class 44.—Still and aerated table water, distilled water. For washing out the system in kidney and liver disorders, also gout and dyspepsia.

San Pellegrino (near MILAN, ITALY).—Diuretic. Calcium and magnesium sulphates, some carbonate with trace of chloride, also lithium. Mineral salts amount to 1·264 g. per litre.

Santenay (FRANCE).—The gas given off at the spring by this lithium water contains 10·16% helium with traces of neon.—Prof. C. Moureu, *Chem. & Drugg.*, i/1923, 869.

Saratoga (U.S.A.).—"Congress" and "Hathorn" springs.—Alkaline, saline. A mild aperient in dyspepsia, skin affections, diseases of the stomach, liver, kidney, and blood, constipation. Imported.

Siculia Water from Malnasi, Transylvania. A Rumanian water advertised for gout, rheumatism and lung and throat diseases.—*Chem. & Drugg.*, i/1922, 68.

Slanic Spa (RUMANIA).—Rich in carbon dioxide. Alkaline. Stimulates secretion by content of sodium chloride. Antacid.

Soulac-sur-Mer (MEDOC, GIRONDE, FRANCE).—Health resort. Sea air.

Spa (BELGIUM).—Ferruginous. Anæmia, uterine and nervous disorders, rheumatism, gout. Summer, and imported.

Strathpeffer.—See **Health Resorts**.

★**Sulis**. T.M. 46734 and 269024, Class 44 (Bath Water, aerated).—Aperient table water. Calcium and sodium sulphates, magnesium and sodium chloride. Gives a radio-active emanation.

★ **Tansan.** T.M. 316950 and 319507, Class 44.—A Japanese water, radioactive. Radio-activity stated to be 31 Mache Units. A tonic table water. Imported.

Tarasp (LOWER ENGADINE, SWITZERLAND).—St. Lucius Spring.—Sulphated alkaline. Rich in sodium sulphate, bicarbonate and chloride. Diuretic. Useful in chronic catarrh of the stomach, dyspepsia, gastralgia, habitual constipation, disorders of nutrition, obesity. June 1st to September 15th. Imported. Description.—*Brit. med. J.*, ii/1921, 328.

Thonon (LAKE LEMAN, FRANCE).—Alkaline, carbonated and benzoated (balsamic resins are contained). In liver complaints and urinary diseases. Imported bottled.

★ **Tonalka.** T.M. 262400, Class 3; 449507, Class 44.—An alkaline tonic aperient water. Supplied in syphons and bottles.

Trefriw Wells near Llandudno, contain iron in ferrous state. One well showed iron in this form equivalent to 2.21 grains per ounce of crystalline ferrous sulphate, the other 1.42 grains. Dose: $\frac{1}{2}$ oz. twice daily.—*Brit. med. J.*, i/1919, 712.

Tsagesi (GRECIAN).—Chalybeate.—Ph. Notes.

Uriage (FRENCH ALPS).—There are two springs, an iron spring containing bicarbonate of calcium and sulphates of calcium and magnesium, and a sulphur spring containing hydrosulphuric acid and sodium monosulphide. Useful for scrofulous children, congenital syphilis, glandular diseases, skin diseases and neurasthenic conditions.—*Lancet*, i/1924, 1037.

The waters considered to facilitate absorption of mercury.—D. Freshwater, *Practitioner*, March, 1912.

Vals (ARDECHE, FRANCE).—Springs: Madeleine, Précieuse, Désirée, Rigolette, St. Jean. Alkaline, acidulated. (Contents vary with the spring.) Rheumatism, anæmia, skin affections. Imported.

Vange (ESSEX, ENGLAND).—Resembles many aperient Continental waters, e.g., those associated with Franz Josef, Hunyadi Janos and Seidlitz.

The true Vange Water (Farmer Cash's Well) is much more concentrated than Hockley Water. It contains calcium carbonate 46.5, calcium sulphate 88.7, magnesium sulphate 495, potassium sulphate, 38.4, sodium sulphate 144.8, and sodium chloride 60.3 parts per 100,000. The Hockley Water contains calcium carbonate 46, calcium sulphate 57, magnesium sulphate 144 and sodium chloride 61 parts per 100,000. Analysis of other Essex springs.—J. C. Thresh, *Pharm. J.*, ii/1922, 557.

The supply of the true sulphated water is about 200 to 300 gallons per day.—J. C. Thresh, *Lancet*, ii/1922, 1258.

Vernet-les-Bains (PYRENEES ORIENTALES, FRANCE).—Sulphate. Sodium sulphate and thiosulphate. Constipation, skin affections, anæmia. May to October, and imported.

Vernet-les-Bains Springs described.—*Lancet*, ii/1922, 825.

★ **Vichy.** T.M. 312342-3, 46155 and 46158, Class 44. (ALLIER, FRANCE.) Springs: Grande Grille, Hôpital, Célestins, Parc.—Alkaline, acidulated gravel, chronic urinary affections, diabetes, female complaints, gout, rheumatism, facilitates digestion. May 15th to September 30th, and imported.

The gas given off at the spring by the mineral water at the source Chomel contains 0.16% nitrogen.—Prof. C. Moureu, *Chem. & Drugg.*, i/1923, 869.

The composition of Vichy Water, according to Sir James Barr, is, in grammes per litre, bicarbonates of sodium, 5.6, potassium 0.35, lithium 0.012, calcium 0.36, magnesium 0.07, iron (-ous) 0.001, sodium chloride 0.57, sodium sulphate 0.28, silicon oxide 0.06, free carbon dioxide 0.97. The water is isotonic with the blood serum.—*Brit. med. J.*, i/1927, 1063.

Villacabras (SPAIN).—Saline aperient. Sodium sulphate. Obesity and constipation. Imported.

Analysis shows sodium sulphate 78.51, sodium chloride 1.05, magnesium sulphate 2.74, calcium sulphate 1.70 g. per litre. Replaces bitter waters of Germany, Austria and Hungary.—*Lancet*, ii/1915, 184.

Vittel (VOSGES, FRANCE).—Spring, Grande Source.—Alkaline. Sodium and magnesium bicarbonates, sodium, calcium, and magnesium sulphates; carbon dioxide. Uric acid, scrofula, chlorosis, biliary and urinary congestion. In

addition are Source Salée, stronger in magnesium sulphate; Source Marie and Source des Demoiselles, chalybeate. The first two are imported.

★**White Rock** (U.S.A.). T.M. 240106, Class 44.—Lithiated, gaseous Table water.

Woodhall (LINCOLNSHIRE).—Saline, bromo-iodised. Bromide, iodine (free and combined), sodium chloride, arsenic. Gout, sciatica, rheumatism, skin affections, goitre, women's diseases.

A large range of diseases from arthritis to eczema may be treated on orthodox principles.—*Lancet*, i/1909, 1478.

★**Wychia** (DROITWICH). T.M. 274130—Saline. Sodium chloride 11·93 and sulphate 7·89 g. per litre. Droitwich water is distinctly radio-active. Laxative in habitual constipation and plethora. The water is stated to be of specific value in gout, rheumatism and renal dropsy. Dose: $\frac{1}{2}$ to 1 tumblerful, two or three times a day.

Droitwich Brine Baths have no equal for treatment of sciatica and allied affections. Even rheumatoid arthritis is certainly improved and in some cases actually cured. The cures of chronic sciatica are most striking.

Analysis of the brine has shown it to contain 20,000 grains per gallon of saline constituents in excess of that possessed by any other known water. The actual figures are: sodium chloride 21761·8, magnesium chloride 2·5, calcium sulphate 91·1, aluminium sulphate 14·4, sodium sulphate 342·7, sodium iodide 0·208; total salts to an imperial gallon, 22212·8 grains.

The brine acts possibly by absorption through the skin because the acidity of the urine is diminished, the output of uric acid being eventually lessened. Patients soon remark the change of colour in their urine, and the absence of pink deposit so well known in lithæmia. Urates are increased at first, and afterwards, as the urine becomes alkaline, they become diminished. The brine acts as a powerful uric acid solvent. The radium emanation contained has something to do with this. Wonderful results in neurasthenia. Certain diseases are aggravated by the brine, e.g., malignant disease. The brine will cure almost every variety of uric acid disease, both those belonging to the collæmic, and also to the arthritic group.—*J.R. Army med. Cps*, July 1911.

Imported bottled mineral waters classified according to chemical composition.—A. E. Mix and J. W. Sale, *J. Amer. med. Ass.*, ii/1925, 1964.

BRITISH SPAS AND CLIMATIC HEALTH RESORTS

SPAS

The British spas are distinguished by their invigorating tonic quality, and are to be preferred for those needing a cooler and more stimulating treatment than that offered by the continental spas. They possess most of the waters necessary for preventing ill-health and for relieving the disorders associated with a northern climate, offering treatment both for maladies of congestion and of debility, and are all situated in beautiful and interesting surroundings, thus providing necessary supplementary mental refreshment. In the following list of the more important spas the approximate proportion of the principal constituents in parts per million of the water, and the season for each spa is indicated. However, in summer and autumn all are in season. Spring is a favourable season for waters, especially in children, while chilly, elderly and rheumatic people are often most benefited by autumn and winter treatment. A course of baths will often fully restore the functions of the skin, while both baths and waters increase the natural elimination of waste products, and appropriate bath

can *increase* the efficiency of the heart muscle and stimulate or soothe the circulatory and nervous systems. Besides these effects in regulating disordered functions and a certain *intensive* influence in chronic disease, spa treatment is also *alterant*, and is therefore beneficial in digestive, rheumatic and arthritic diseases. The treatment is ambulatory. The treatment at different spas is suited to two constitutional types of chronic illness:—Type A. Deficiency of body heat; chilly subjects with poor circulation, languid and anæmic, circulatory hypotension. Type B. Excess of body heat; warm subjects, florid and congested, hyperpiesia, circulatory hypertension.

Bath (SOMERSET).—One of the warmest winter resorts. Climate sedative, reinforcing the effect of thermal treatment; cooler and more invigorating on the Downs, 200 feet above the city. Hyperthermal radioactive gaseous waters; diuretic, solvent, promoting elimination of uric acid; pools and manipulation douches, aeration and vapour baths. *Indications:* Type B, most rheumatic conditions with inactivity of the skin and circulation requiring *thermal* heat and manipulation and re-education; indolent and indurated skin affections, constipation and chronic forms of colitis, certain functional and degenerative conditions of the heart, hepatic dysfunctions—*inhalation* of natural radio-active gas for catarrhal and gouty affections; season all the year. Calcium sulphate 1400, sodium sulphate 300, magnesium chloride 200, calcium carbonate 100, strontium, iron, silica, aluminium and bromine, gas 52 parts by weight, mainly nitrogen and carbon dioxide with argon, neon, helium and niton, 104° to 120°.

Bridge of Allan (STIRLINGSHIRE).—Tonic-sedative, climate mild and equable even in the winter months, bracing and invigorating on the moorland, dry porous soil. Salt waters with calcium and bromine, which are nearly isotonic, mildly aperient, diuretic and alterant, also used for baths, douches and inhalation. *Indications:* Types A and B, chronic rheumatic diseases, digestive and respiratory catarrhs, bronchial asthma, hepatic dyspepsia. Season, all the year. Sodium chloride 5042, calcium chloride 3659, magnesium bicarbonate 125, calcium sulphate 316, sodium bromide 72.

Builth Wells (BRECON).—Mild climate; strong saline waters, hypertonic, aperient and alterant, the strongest used for drinking in Britain containing calcium salts and bromine; also a sulphur water and a chalybeate. *Indications:* Dyspepsia and constipation, catarrhal and tuberculous affections.

Buxton (DERBYSHIRE).—Climate very tonic, bracing, dry and keen, pleasantly cool in summer, atmospheric humidity low owing to dry subsoil. Gaseous sub-thermal nitrogenous waters, diuretic, alterant; also chalybeate. Pools at 83° and at 98°, aeration, manipulation and peat baths. *Indications:* Type A, rheumatic conditions, arthritis and peri-arthritis, especially in anæmic and depressed rheumatic subjects; fibrositis, gout, the uric acid diathesis, urinary gravel and calculus and some cardiac cases, convalescence, anæmia, asthma and malaria. *Contra-indications:* Unsuitable for respiratory catarrhs, heart disease or nephritis, debilitated subjects with poor reactive qualities. Season, May to September. Calcium carbonate 200, sodium chloride 40, iron and manganese; gas—nitrogen 59·8%, carbon dioxide 40·2%.

Cheltenham Spa (GLOUCESTERSHIRE).—One of the most sheltered inland climates of the British Isles; sedative. Sulphated salt waters with some alkali, mildly laxative, metabolic. Manipulation douche, aeration, brine and paraffin wax baths. *Indications:* Type B. Gastro-intestinal and cardiovascular disorders, acid dyspepsia, constipation, hæmorrhoids, glycosuria and obesity, gastro-hepatic and bronchial catarrhs, high blood pressure and degenerative changes of the blood vessels, convalescence, insomnia. Season, all the year round. Twin-salt—sodium sulphate and magnesium sulphate each 3800, calcium 1200. Lansdowne-sodium—chloride 5600, with half as much sodium sulphate. Hepatic-sodium—bicarbonate 400. Renal—magnesium and calcium saline.

Droitwich Spa (WORCESTERSHIRE).—Fairly equable climate, with remarkable freedom from fog and snow; tonic-sedative, the general atmosphere restful although not relaxing; summers pleasantly warm, winters not cold. Saturated brine radioactive baths for stimulant surface treatment, sub-thermal and thermal pools, aeration and effervescent baths and douches. *Indications:* Type A.

Fibrositis, sciatica, lumbago, neuritis, rheumatoid arthritis and osteoarthritis paralysis, functional weakness of heart and circulation with low blood pressure peripheral stasis. Season, all the year. Sodium 117,312, magnesium 156, calcium 1,328, chlorine 180,155, bicarbonate 11, sulphate 5,014, radon 0.2 m.m.c. per litre and 12.4 m.m.c. in the dissolved gases.

Harrogate (YORKSHIRE).—Very tonic, bracing climate with freshness and elasticity of the air, relative humidity low, winters cold but not bleak, summers tempered and fresh. Strong and milder sulphur-saline waters, laxative, stimulant, metabolic and saline, chloride of iron and pure chalybeates, deposits of medicinal mud. Sulphur, saline, douche, vapour and peat baths. *Indications:* Type B. A tonic spa for hyperpiesis, hepatic disorders, glycosuria, constipation, arterial hypertension, congestive arthritis of middle life, menstrual disorders and chronic malaria. Season, spring, summer and autumn. Saline—sodium chloride 13,300, sodium sulphide 150, barium chloride 100, hydrogen sulphide 37,000 volumes. Alkaline sulphur—sodium carbonate 450, sulphide and very little salt. Tonic chalybeate—saline and iron carbonate 150, and stronger with iron carbonate 500.

Leamington Spa (WARWICKSHIRE).—Mild, equable and dry climate, sedative. Strong hypertonic salt-sulphate water with predominance of chloride and calcium, aperient and diuretic and mild saline, hypotonic water, diuretic. Saline, aeration and Turkish baths. *Indications:* Type B. Digestive and toxic disorders, chronic autotoxæmia, obesity, arterial hypertension. Season, spring to autumn. Strong saline—sodium chloride 12,451, calcium sulphate 2842, magnesium sulphate 377.

Lisdoonvarna (CO. CLARE).—Fresh, invigorating climate, the soft pleasant air combining qualities of sea, mountain and moorland. Two sulphate and two chalybeate waters. Sulphur baths. *Indications:* Type A. Convalescence, chronic catarrhs of the stomach and bile ducts, disorders of metabolism, chronic gouty and rheumatic affections and neuritis. Season, summer and autumn.

Llandrindod Wells (RADNORSHIRE).—Pleasant and invigorating, tonic-sedative air. Mild saline springs—hypotonic, saline sulphur water—solvent, eliminant, metabolic and chalybeate waters. Saline, douche and aeration baths. *Indications:* Type A. Chronic gastro-intestinal catarrhs and toxæmias, mucous colitis, rheumatic disorders and asthenic states. Season, summer and autumn. Saline—sodium chloride 1800 to 6200, calcium chloride 400 to 1300, lithium chloride and carbonate 1000. Salines with hydrogen sulphide 7000 to 9500 volumes.

Llanwrtyd Wells (BRECON).—Climate is not humid, the air being very pure and tonic-sedative. Most remarkable water of its kind on account of its constancy of flow and great strength in unassociated sulphur; diuretic and alterant. Sulphur baths. *Indications:* Type A. Rheumatic and skin affections, tuberculosis of glands, bones and joints in children, for the overworked and neurasthenic. Season, summer and autumn.

Lucan Spa (CO. DUBLIN).—Mild sheltered climate. Alkaline sulphur waters. *Indications:* Chronic rheumatism and gout, eczema, psoriasis, chronic toxic conditions.

Moffat Spa (DUMFRIES-SHIRE).—Very pure and equable air, bracing especially during the spring and autumn—tonic-sedative. Hypotonic, saline sulphur waters, diuretic, alterant, also an uncommon form of iron water in Hartfell mountain, 4 miles away, for debility and anæmia. Sulphur baths. *Indications:* Type A. Chronic rheumatism and gout, atonic indigestion and tropical liver chronic toxæmias and bladder and renal cases where diuresis is indicated, convalescence. Season, summer and autumn. Sodium 392, calcium 61, magnesium 25, barium 15, strontium 9, potassium 4, lithium 0.5, chloride 721, bicarbonate 141, sulphate 14, bromine 7, sulphide 7, nitrate 3, iodide 0.2 and silicic acid 19.

Nantwich and Northwich (CHESHIRE).—Equable and mild climate with low rainfall, tonic-sedative. Concentrated, stimulant brine baths. *Indications:* Type A. Rheumatism, arthritis, sciatica, lumbago, poor circulation and nervous debility. Season, summer.

Strathpeffer Spa (ROSS-SHIRE).—The most northerly of the British spas. Sheltered, tonic-sedative climate, but fresh and invigorating on the upper slopes, essentially a tonic spa with its cool, long summer days. Strong non-aperient sulphur waters with calcium, diuretic, alterant, also a chalybeate for neurasthenia and anæmia. Sulphur, douche and peat baths, inhalations. *Indications:* Type A. Atonic, digestive or nervous conditions, chronic senile rheumatism.

arthritis, obscure toxæmias, bone and skin affections of toxic origin, hepatic congestion and mucous colitis. *Contra-indications*: Acute rheumatic and gouty disorders, persistent high blood pressure. Season, summer and autumn. Calcium sulphate 271 to 729, calcium carbonate 100 to 214, magnesium sulphate 570 in one water, hydrogen sulphide 18,000 to 69,000 volumes per million.

Trefriw (CAERNARVONSHIRE).—Soft but invigorating climate with combination of mountain and sea air, cold, clear and still. Very strong acid ferrous-sulphate waters, alterant and tonic, very easily assimilated. Acid iron baths and compresses. *Indications*: Type A. Convalescence, illnesses of mal-assimilation, anæmia and debility, atonic arthritis of middle and later life. Season, July to September. Iron protosulphate 2168, calcium sulphate 1013, aluminium sulphate, 1103 and silicates 170.

Woodhall Spa (LINCOLNSHIRE).—One of the driest climates in England, fresh and bracing air. Hypertonic bromo-iodine salt waters, unsuitable for internal use without dilution, metabolic, eliminant. Salt baths, fango packs and inhalations for respiratory diseases. *Indications*: Type A. Osteoarthritis, muscular rheumatism, fibrositis and peripheral neuritis, diseases peculiar to women, chronic glandular enlargements, exophthalmic goitre, Graves' disease. Season, summer and autumn. Sodium chloride 14,700, calcium chloride 3600, sodium sulphate 1300, bromine 50 and iodine 24.

MARINE HEALTH RESORTS

(i) NORTH-WESTERN GROUP

The climate of this region is an "ocean climate," very temperate, equable by day and night, warm in winter, cool in summer; very small daily range of temperature, winter average 42°F., apt to be stormy, but fogs and mists are uncommon.

NORTH WALES SECTION

Anglesey.—Bracing in the north and sheltered along the straits. For bronchial and heart troubles but not asthma.

Bangor.—Recommended for anæmia.

Colwyn Bay.—Sheltered climate, rather dry for a westerly coast resort, frosts infrequent. As a winter resort for aged and infirm persons and delicate children, respiratory troubles, heart and kidney diseases.

Llandudno.—Both mild and bracing climate, with low humidity; winters moderately sunny with little frost or fog. Well suited for patients suffering from chronic maladies of lungs, heart and kidneys, especially in the winter months.

Llanfairfechan.—Bright and sunny, bracing in summer.

Penmaenmawr.—Pleasant, tone-giving climate in summer, sheltered in winter. Suitable for convalescence, and those suffering from chronic chest affections, anæmia and irritable neurasthenia.

Rhyl and Presattyn.—An open, breezy and sunny resort with very low rainfall. Favourable for chronic respiratory catarrhs and convalescence.

ENGLISH SECTION

Blackpool.—Climate very tonic, strong winter winds. Suitable in spring and early summer for nervous and mental fatigue, insomnia and convalescence, chronic catarrhs of the upper respiratory passages, tuberculous adenitis, phthisis. Not suitable for bronchial catarrhs, renal and cardiac diseases and irritable skin affections or invalids in summer.

Grange-over-Sands.—Sunny, sheltered, southern aspect. Rather oppressive in summer. Recommended in spring and early winter for chest cases, high blood pressure, heart troubles, wasting and nutritional disorders. Not suitable for rheumatism, nasal catarrhs or hay fever.

Lytham St. Anne's.—Bright and mild in winter with very little frost. The pure, fine western air is favourable for chronic lung and kidney affections, nervous and circulatory overstrain, convalescence and for catarrh and rheumatism in summer.

Morecambe and Heysham.—Fine, sedative north-western air, suitable in winter for bronchitis, asthma, emphysema, phthisis, early stages of degenerative diseases of the kidneys, blood vessels or nerve centres.

Seascale.—Very tonic, well-suited for convalescents requiring mountain air, especially those recovering from pulmonary and bronchial affections, nervousness and insomnia.

Southport.—Sunny, comparatively dry and equable. Summer atmosphere extremely clear and free from micro-organisms. In autumn, winter and spring, for chronic bronchial catarrh, emphysema in elderly persons, chronic phthisis, asthma, tropical diseases.

SCOTTISH SECTION

Firth of Clyde and Ayr.—Very mild and inclined to humidity. A splendid convalescing climate at all seasons, favourable for respiratory and nervous affections. Contra-indicated for rheumatism.

Oban and the West Highlands.—Typical Atlantic climate. For those who require a soothing and restful climate, such as sensitive brain-workers.

Prestwick.—Little snow and no fog; westerly winds, but enjoys considerable shelter. April and June are dry months with much sunshine. For children with glandular, abdominal or surgical tuberculosis, elderly people and invalids, asthma or bronchial rheumatism.

Rothsay.—Characteristic western sedative climate, warmer in winter and cooler in summer than the average for Scotland. Beneficial to chilly and elderly subjects who are sensitive to winter cold and changes of temperature, and for chronic heart, bronchial and kidney affections.

ISLE OF MAN SECTION

Douglas.—The climate is warmer and more equable than might be supposed, exposed only to sea breezes. Excellent in spring, early summer and September for delicate persons needing pure marine air, with protection against sudden changes of temperature.

IRISH SECTION

Bray and Greystones.—Dry bracing climate, sunny at all seasons, protected from westerly winds.

Howth.—Mild and salubrious air.

Kingstown.—Equable climate with low rainfall, especially in winter, favourable for diseases of the respiratory tract; the autumns are fine. The air is especially beneficial for nervous disorders with depression, insomnia and convalescence.

Newcastle.—A beautiful resort with fine, bracing air. Rainfall rather heavy but soil dries rapidly. Winter climate mild, sheltered from strong winds; spring and autumn are favourite seasons.

Portrush.—Remarkably equable climate with cold, bracing and exhilarating northerly winds. Beneficial in cases of depression, neurasthenia, insomnia and convalescence.

Rostrevor.—A winter and spring resort for bronchial and pulmonary diseases, and for cases requiring rest in invigorating but sedative air.

(ii) SOUTH-WESTERN GROUP

These resorts enjoy the warmest winter climate of the United Kingdom; the average temperature comes within 4° of Nice, but differs widely in daily distribution of heat. The south-west is characterised by warm nights, low daily range and equability.

SOMERSET SECTION

Clevedon.—A quiet comfortable resort with a sedative, sheltered, sunny and comparatively dry climate. Suitable for elderly people and children, chronic lung conditions other than phthisis, nervous excitability and insomnia.

Minehead.—Mild and invigorating, tempered in summer by sea and mountain breezes. Suitable for chronic respiratory catarrhs, except in February and March, kidney diseases, arterial hypertension, nervous exhaustion and insomnia, forms of rheumatism. Unsuitable for asthma, tuberculosis or liver disorders.

Weston-super-Mare.—Mild, but bracing climate. Medical baths. Suitable for defective nutrition and "tone" of delicate children, convalescence requiring a tonic-sedative influence; as an "after-cure" following thermal treatment for chronic rheumatic diseases. Not suitable for hæmorrhagic phthisis or acute disorders.

WELSH SECTION

Aberdovey.—Warmest winter resort on the Welsh coast, facing south, remarkably sheltered climate. In winter and spring for those requiring an equable sedative and restful atmosphere, suffering from respiratory catarrhs or failure of the circulatory or excretory systems. Firm sand, good bathing and fishing.

Aberystwyth.—Open to bracing temperate westerly winds but sheltered from the east. Suitable for nerve exhaustion, insomnia, renal complaints, anæmia, convalescence. Rheumatism, asthma and catarrhal affections are contra-indicated.

Barmouth.—Sheltered without being relaxing. Firm sand and safe bathing. Suitable especially in early spring and late autumn for chronic phthisis and bronchitic cases, convalescents and nervous cases requiring mild air.

Barry.—Mild but invigorating. Firm sandy beaches with good sea and surf-bathing. Favourable for convalescent nervous cases and delicate children. Catarrh, rheumatism and asthma are contra-indicated on account of prevailing westerly winds in winter.

Porthcawl.—Pleasantly bracing with mild sunny air.

Pwllheli District.—Winter climate exceptionally warm and equable.

Swansea and Mumbles.—Fine bracing air and sea-bathing till October.

Tenby.—Insular climate. Suitable in the winter months for chronic ailments of middle and later life requiring even warmth, especially chest cases and bronchial affections.

DEVONSHIRE AND DORSET SECTION

North

Ilfracombe.—Invigorating climate for respiratory affections (excepting phthisis), convalescence, elderly people and those returned from tropical climates. Unsuitable for catarrh and rheumatism.

Lynton and Lynmouth.—Moorland and sea air, and northerly aspect producing bracing and invigorating summer climate.

South

Dartmouth and Slapton.—Recommended for those who require a kind and equable climate with shelter from cold winds.

Exmouth.—Suitable for elderly people or those returning from hot climates, delicate or tuberculous children.

Lyme Regis and Sidmouth.—Tonic-sedative climate enjoying much sunshine in winter months. Winter climate suitable for convalescent and delicate elderly persons, bronchial catarrh and emphysema, high blood pressure, incipient or chronic renal disease. Lyme Regis is unsuitable for heart cases.

Paignton and Brixham.—Easterly aspect, more bracing than Torquay, equable and sunny, exceptionally mild in winter, good bathing on firm sands. Suitable for delicate persons needing a mild but bracing air, especially for circulatory or respiratory troubles.

Salcombe.—One of the mildest climates in the country. In spring and winter for delicate persons, especially for emphysema, phthisis, bronchitis and invalids from hot countries.

Seaton, Beer and Axmouth.—More "open" character winter climate than south Devon resorts; enjoy a cool land breeze in hotter weather. Gentle exercise on the level suitable for convalescent heart and lung cases and high arterial tension.

Teignmouth.—South-easterly exposure produces a mild but bracing climate, sedative and stimulant. An invigorating and restful summer sea-bathing health resort. Suitable all the year round for delicate children, and elderly persons requiring pure but not too bracing air.

Torquay.—Beautifully situated, mild, soft, equable climate, warm and sunny in winter, comparatively cool in summer. Medical baths. For laryngeal and bronchial respiratory catarrhs, bronchial asthma, emphysema, chronic phthisis; endocarditis, nephritis.

CORNWALL SECTION

North

Boscastle, Tintagel, Port Isaac.—Boscastle a little more sheltered than exposed Tintagel, and is recommended for nervous breakdown and overstrain.

Bude.—Healthy, bracing resort excellent for children. Strong Atlantic winds render it less suitable for invalids in winter. For bronchial catarrh, early phthisis, anæmia, debility.

Newquay.—Bracing climate. Suitable for tuberculous children, early phthisis and asthma, convalescence. Not suitable from June to March for catarrhal chest conditions, heart cases and later stages of phthisis.

St. Ives, Carbis Bay.—Winter warmth and equability of temperature but bracing. Sunshine stated to be exceptionally rich in ultra-violet rays.

South

Falmouth.—The mild, sedative climate is more equable than the south of France or Madeira. For lowering the output of nervous and mental energy, acting as a hypnotic in insomnia. Situated between two waters, producing a freshness of the air. Nervous exhaustion, chronic bronchial and laryngeal catarrhs, renal disease.

Fowey, Looe.—Sunny, sheltered climate, suitable at all seasons for invalids and delicate persons with diminished margin of adjustment, convalescents from bronchial pulmonary heart and kidney affections.

Lizard, Mullion.—Recommended for a restful holiday and sea-bathing.

Penzance.—Occupies a sheltered position facing south-east. Suitable for chronic forms of pulmonary disease, slow degenerative changes of the kidneys, and invalids.

Scilly Isles.—Very warm in winter. Windy and sunny, producing a sense of space and remoteness for the tired brain-worker.

IRISH SECTION

Ballybunion.—Good, safe bathing on firm sands. Seaweed baths.

Bundoran.—Fine Atlantic air. Open sea bathing in a rather warm sea.

Enniscrone.—A pleasant holiday and health resort, extensive sands and safe bathing. Hot sea-water baths for treatment of rheumatic and other cases.

Glengariff.—A sheltered climate.

Kilnee.—A typical Atlantic climate.

Killarney.—Soft, genial air for those who are too sensitive to bracing winds, mountain climbing for the more vigorous.

Queenstown.—Moist and windy climate but uncommonly mild and equable. Suitable in winter and spring for cases of pulmonary delicacy or catarrhs of the respiratory passages and convalescents requiring entirely soothing and sedative atmosphere.

Tramore.—Long stretch of firm sands and excellent bathing. Climate favourable for debility, including chronic rheumatic disorders.

CHANNEL ISLANDS SECTION

Jersey.—Mild, equable, sunny climate but experiencing north-easterly and easterly winds in spring. In late autumn and winter for delicate children, chilly and bronchitic elderly subjects. The even and oceanic climate provides an easily available alternative to a sojourn in Madeira or the Riviera.

Guernsey.—Warm, equable climate, prevailing winds, south-westerly except in March and April. More bright sunshine than any other part of the United Kingdom. Indicated for all forms of delicacy or chronic illness requiring sunshine and warmth (except in March and April). Unsuitable for persons sensitive to humidity.

(iii) SOUTHERN GROUP

These resorts are 2° cooler in winter than the south-western group but are more sunny. The rainfall diminishes from west to east, and it therefore occupies an intermediate position in regard to humidity.

EASTERN DIVISION. Winters very mild, sunny and dry.

Bognor.—Firm sand and good bathing. Suitable for delicate, catarrhal and bronchial subjects, cardiac convalescence, insomnia and neurasthenia.

Brighton and Hove.—Decidedly bracing. Beneficial for people run down physically or mentally, delicate children, convalescence. Hove is slightly more sheltered.

Littlehampton.—Sunny, equable climate but more bracing than most south coast resorts. Recommended for catarrhal conditions with debility, neurasthenia and insomnia.

Seaford.—Rather bracing, with occasional south-west gales in winter. Air is very beneficial to children for chest and nerve complaints and convalescence.

Southsea.—Equable and healthful both summer and winter. Clean, bright atmosphere with few sea fogs. Suitable for delicate children, anæmia and debility, rheumatism, asthma, and bronchial, catarrhal and chronic phthisis.

Worthing.—Sheltered climate, one of the most sunny of the south coast resorts. As a winter resort for cases of glandular tuberculosis, chronic respiratory affections, bronchial asthma, convalescence after influenza, rheumatoid arthritis, chronic rheumatism.

WESTERN DIVISION. Summers sunny, pleasantly cool, fairly dry and equable, winters very mild and sunny.

Bournemouth and Christchurch.—Good bathing. Winter resort for delicate and debilitated subjects. Recommended for Bright's disease, malaria, catarrhal and pulmonary complaints, and bronchial asthma.

Poole.—Some bracing qualities. Fine sandy beach. Recommended for pre-tubercular children, chronic bronchial catarrhs, hyperpiesia, general convalescence. Contra-indicated for dyspepsia, rheumatoid arthritis and skin affections.

Swanage.—Open, easterly aspect, but sheltered on the north, south and west. Good sandy bathing beach. Favourable at all seasons for chronic phthisis and bronchial catarrh, asthma, neurasthenia and insomnia.

Weymouth.—Excellent resort for delicate children, nerve cases, convalescents and respiratory catarrhs.

ISLE OF WIGHT

Ryde.—Exceptionally pure and fairly bracing air; sheltered from the south-west and channel fogs. Indicated for elderly and delicate persons, chronic bronchial and pulmonary cases, and cardiac convalescents.

Sandown.—Very sunny, moderately bracing, almost entirely free from fogs. The early winter months are mild. Good safe bathing. From June to December recommended for many forms of delicacy and incipient and chronic disease.

Shanklin.—Mild, dry, and very sunny. A chalybeate water is employed both for drinking and baths. For "lymphatic" and delicate children, anæmia, debility, chronic renal complaints. Air beneficial for catarrh, irritable neurasthenia and insomnia.

Ventnor.—Remarkably equable climate with warm winters and comparatively cool, fresh summers. Beneficial at all seasons in pulmonary tuberculosis, chronic bronchial and asthmatic catarrh. Favourable for children with nervous instability, hypersensitive invalids and for insomnia. Contra-indicated for eczema, neuralgia, constipation and, on account of its hilly formation, for serious heart or lung weakness.

(iv) SOUTH-EASTERN GROUP

The sedative and tonic climate is suitable for robust subjects. Sunshine records for the winter months average from $2\frac{1}{2}$ hours per diem in November to $4\frac{1}{2}$ hours per diem in March.

NORTHERN SECTION. Dry, sunny, bracing climates.

Broadstairs.—Suitable from spring to late autumn for general debility, convalescence, pre-tubercular conditions, surgical tuberculosis, chronic catarrh, asthma and cardiac rheumatism. Contra-indicated for pulmonary tuberculosis.

Clacton-on-Sea.—Certain shelter from east winds make the winters often warm and sunny. Suitable for glandular tuberculosis, convalescence, certain types of neurasthenia. Contra-indicated for bronchitis and all acute or advanced conditions.

Dover.—Invigorating, tonic climate recommended for convalescence and catarrhal conditions. Too hilly for heart cases, unless confined to the sea front.

Frinton.—Recommended in summer and autumn for recuperation, convalescence and sufferers from enlarged glands.

Herne Bay.—One of the driest and sunniest summer coast resorts. South-westerly winds prevail except in spring. Suitable for early tuberculosis of the lungs and glands and bone cases in children.

Margate.—Very tonic air, northern aspect producing cold variations. Tuberculous diseases of bones, joints and glands, chronic post-nasal catarrh, chronic empyema with sinus, anæmia in children, convalescence, old malaria, languid neurasthenic conditions, especially in early summer and autumn. Not suitable for cases of active pulmonary tuberculosis.

Southend-on-Sea. Driest winter health resort in England with invigorating air. Ozone-iodised baths. Beneficial to delicate children for convalescence, chronic fatigue, insomnia, pulmonary tuberculosis if not associated with catarrh, asthma. Contra-indicated for chronic catarrhs, bronchitis and emphysema.

Ramsgate.—Invigorating, more sheltered than Margate; winter comparatively warm. Indicated for delicate, anæmic and pre-tubercular children, convalescence, early pulmonary tuberculosis and some forms of chronic renal trouble.

Walton-on-the-Naze.—Easterly marine air, very good for young people especially if susceptible to respiratory catarrhs, tuberculosis of glands or joints and for convalescence and insomnia.

SOUTHERN SECTION. Dry and invigorating, with sunny, mild, dry winters.

Bexhill.—Suitable for convalescent and anæmic persons, debility resulting from tropical diseases, chronic catarrhs of the upper respiratory tract and some cases of asthma.

Eastbourne.—Tonic climate with few local fogs. Suitable for delicate children. Medical and surgical convalescents; asthma, nervous exhaustion and insomnia except in the spring.

Folkestone and Hythe.—Fairly warm for an easterly aspect, bracing; land mists and fog are rare. Recommended in summer and early winter for bronchial catarrh, some rheumatic cases, nervous insomnia, convalescence, anæmia and debility.

Hastings and St. Leonards.—Temperate, sheltered climate, but more tonic and bracing on higher ground of St. Leonards. Seaweed and other baths. Suitable for chronic catarrhs in children, bronchial catarrh, asthma, insomnia, glandular tuberculosis and post-tropical delicacy of children.

(v) EASTERN GROUP

A group of sunny, bracing summer resorts. The prevalence of south-westerly winds makes many of them suitable for delicate persons in autumn.

SOUTH ENGLISH SECTION. Dry and very bracing.

Cromer.—Tonic with mild autumns. For tuberculosis, respiratory catarrhs, asthma, anæmia, debility, convalescence. Contra-indicated for vascular hypertension, border-line mental cases and heart disorders.

Felixstowe.—Southern aspect, winters sunny. Beneficial for tuberculosis of glands and joints in children, anæmia, general debility and incipient phthisis, and, except in spring, for respiratory catarrhs.

Great Yarmouth.—Keen and bracing. Fine sands and bathing, excellent for fairly robust and atonic subjects, for languid nervous cases, children with tubercular adenitis needing increased metabolism. Contra-indicated in winter for bronchial catarrh and rheumatism.

Hunstanton.—Invigorating, fresh, sunny but more sheltered than neighbouring places. Good bathing. Well suited for convalescents. In late autumn and winter assists recovery of natural resistance to catarrhal and tuberculous invasion but is too bleak in March and April. A chalybeate water at Ringstead one mile away. Not recommended for rheumatism or asthma.

Lowestoft.—Sunny and invigorating climate. October to December often bright and dry. Warm and pleasant summer and autumn resort. For convalescence, chronic catarrhs, malnutrition, tuberculosis of glands and joints, whooping cough, nervous exhaustion and insomnia. Unsuitable for respiratory and cardiac cases requiring a softer sedative air.

Mundesley.—Tonic climate. Good sands and bathing. In summer and autumn for all conditions requiring invigorating air.

Sheringham.—Tonic air suitable in summer for chronic tuberculous affections, nervous exhaustion, insomnia, catarrh and rheumatism.

Southwold, Aldeburgh and Thorpeness.—Dry, sunny, bracing climates.

NORTH ENGLISH SECTION

Bridlington.—Rather windy. A muriated chalybeate water. Suitable in summer and autumn for convalescence, atonic nervous exhaustion and insomnia. Contra-indicated in phthisis, renal diseases and rheumatism.

Cleethorpes.—Fine, bracing, dry, sunny summer and autumn. Excellent for anæmic and debilitated convalescents.

Saltburn-by-the-sea.—Moist and sheltered in the valley but dry and bracing on cliffs. Firm sand, beach one of the finest in Europe. Hot sea-water and brine baths. Recommended for malnutrition and nervous irritability in children and chronic rheumatic affections.

Scarborough.—Bracing but warm summers, easterly winds and mists in spring. Two tonic and aperient chalybeate waters useful in some skin and kidney diseases, dyspepsia and chronic rheumatism. Beneficial in cases of catarrh, nervous exhaustion and insomnia.

Sutton-on-Sea and Mablethorpe.—Bracing and dry climate, recommended particularly in autumn for convalescence, neurasthenia and insomnia, but not suitable for rheumatic cases.

Whitby.—A summer resort with strong easterly airs combined with those of neighbouring moorland.

Tynemouth.—Exceptionally bracing and comparatively dry climate. Excellent stimulant to metabolism. Salt and sea-water baths beneficial for traumatic rheumatism. Contra-indicated for respiratory and renal diseases.

SCOTTISH SECTION. Very dry and sunny. Cool, bracing summers.

Cromarty and the Moray Firth.—Lowest rainfall in Scotland. Beneficial to respiratory catarrhs, asthma and neurasthenia. Winters relatively warm.

Arbroath and Carnoustie.—Good sands and bathing.

Dunbar (Firth of Forth).—Dry soil, fine exhilarating air. Particularly advantageous in autumn for convalescents.

Montrose.—Pure, clean, invigorating, dry resort for summer and autumn.

Nairn and Lossiemouth.—Sea-bathing and climatic resort for summer and autumn. Atmosphere remarkable for its transparency. Suitable for chronic catarrhs, nervous fatigue, depression, "after-cure" following a course of baths and, in autumn and early winter, for delicate children and asthmatic, debilitated and convalescent adults.

North Berwick.—Favourable for "after-cure," languid neurasthenia, overwork, insomnia and asthma.

Peterhead.—Winter warmer than might be expected. Invigorating, dry, bracing, tonic air, invaluable for debility, atonic dyspepsia and anæmia.

St. Andrews.—One of the most bracing climates in Great Britain. Beneficial in nervous debility and insomnia but not suitable for rheumatism and asthma.

INLAND HEALTH RESORTS

Church Stretton (SHROPSHIRE).—Bracing and invigorating climate but with a tranquillising effect on irritable conditions of the circulatory and nervous systems. A good "after-cure" station; water recommended as table water in gout and rheumatism.

Crieff (PERTHSHIRE).—Gently stimulating as well as sedative climate; suitable for "after-cure," tired and delicate persons and recuperation.

Crowborough (SUSSEX).—Equable and bracing summer climate; resort for most chronic diseases of the respiratory organs, neurasthenia, anæmia, debility and convalescence.

Deeside.—Pure, dust-free and singularly translucent air, and dry, bracing climate. **Braemar** is a sub-alpine climatic resort indicated for debility following operations, convalescence and neurasthenia. Contra-indicated for high arterial tension, heart disease and diabetes. **Aboyne** recommended for slight disorders of heart and breathing.

Dunblane (PERTHSHIRE).—Mild, equable climate even in winter, sheltered from cold winds.

Forres (MORAYSHIRE).—Very mild and dry climate at all seasons. For convalescence, phthisis and rheumatism.

Hindhead (SURREY).—Open moorland with dry and very bracing climate, suitable for convalescence and beneficial to cases of pulmonary tuberculosis and nervous exhaustion.

Ilkley (YORKSHIRE). Close to the moors, 750 feet above sea level. Bracing and invigorating, with a rather mild winter climate. Beneficial in chronic gout and rheumatism, various neuralgic affections, peripheral neuritis, neurasthenia, debility and anæmia. The water is a powerful solvent and diuretic eliminant.

The Malverns (WORCESTERSHIRE).—Extremely pure, bracing and rarefied air; comparatively dry and mild winter climate; summers fairly cool. A hill-side climate resort for delicate and elderly people, chronic respiratory diseases, delayed convalescence and nervous exhaustion. Two extremely pure waters are available and recommended for solvent and eliminant properties.

Matlock Bank and Matlock Bath (DERBYSHIRE).—Mild and equable climate. Solvent, non-mineralised medicinal water, valuable in toxic and rheumatic complaints at Matlock Bath. Summer climate of Matlock Bank suitable for some types of chronic pulmonary trouble, chronic renal and cardiac disorders.

Peebles (PEEBLES, SCOTLAND).—Comparatively dry and bracing in summer, cold in winter. Natural saline water beneficial to cases of chronic dyspepsia, hepatic and gouty trouble, especially in autumn and early winter. A good place for a "rest-cure." Asthma is contra-indicated.

Pitlochry (PERTHSHIRE).—Fresh, bracing air, pleasantly cool but sunny in summer. Suitable for convalescence, "rest-cure" and "after-cure."

Ross-on-Wye (HEREFORDSHIRE). Sedative climate at lower levels; more bracing higher up, mild, sunny winters, low humidity in summer. Recommended for catarrh and rheumatism.

Speyside (MORAY, INVERNESS AND BANFFSHIRE).—Semi-alpine climate, fresh, pure, translucent atmosphere with low humidity. Tonic and sedative effect beneficial in nervous and mental fatigue, insomnia, nervous dyspepsia and for "after-cure."

Tunbridge Wells (KENT).—Bracing, sunny climate. Pure air and restfulness favourable at all seasons for some types of neurasthenia.

Yorkshire Dales (N.W.) and Settle.—Bracing air of the moorland recommended for sufferers from abnormal mental, nervous or circulatory fatigue.

For further details see "British Spas, Inland and Seaside Resorts," edited by R. Fortescue Fox (and also for details of New Zealand, South African and Canadian resorts), from which the above notes have been abstracted.

BACTERIOLOGICAL AND CLINICAL NOTES

with Reference to Special Diseases.

Acne Vulgaris. A. Fleming, in 1909, described the bacteriology of acne vulgaris. The acne bacilli are gram-positive organisms which, when seen in pus, are arranged very irregularly. In 44% of the pus films examined only acne bacilli were found. Acne bacilli with staphylococci were present in 53%. The acne bacillus stains less deeply than the cocci. The bacillus grows with difficulty on artificial media. A suitable medium for growing the organism was found to be nutrient agar containing from 1% to 5% of oleic acid. *Cultivation.*—Good results may be obtained by growing anaerobically in broth for 3 weeks and then plating on serum agar with neutral red and about 2% of oleic acid. (*For further details of Fleming's work see Lancet, i/1909, 1035 and Brit. med. J., ii/1909, 533*).

It can also be grown in deep tubes of 2% glucose agar, the reaction of the medium being distinctly acid. Whitish colonies appear after 3 or 4 days at 37° which under a low magnification show a lenticulate shape. The relation of the bacillus to the suppuration in acne has been a matter of dispute.—*M. & R.*

Sudmerson and Thompson use an acid serum agar taking the deeper parts of the comedo in which the bacillus usually predominates, emulsifying this in saline and spreading thinly on the slope so as to obtain colonies to pick off.

Cultivation from the comedo:—T. H. C. Benians recommended for making vaccines to grow simply in a tube of broth—the comedo being removed to same and then covered with sterile oil. *Staphylococcus albus* will be present but is negligible, the bacilli out-growing these cocci in about a week. The conditions are thought to resemble those in a sebaceous gland.—*Lancet, i/1913, 1801*.

The name **Bottle Bacillus** was formerly used as a synonym for acne bacillus, but the work of J. M. H. MacLeod and G. B. Dowling (*Proc. R. Soc. Med., Sect. Dermatol., 1928*) showed that the two are very different organisms. The acne bacillus is a true bacillus present in lesions of acne, and it may possibly be the cause, but, according to MacLeod, it is doubtful whether this has been definitely proved.

The *Bottle Bacillus* these workers have definitely found to be pathogenic and the cause of seborrhœic dermatitis. It is a yeast-like organism belonging to the group of the *fungi imperfecti*, and is related to *monilia*. The name should be discontinued and replaced by spore of Malassez, or *Pityrosporon Malassezii*. It can be stained by the Giemsa method and is pleomorphic, the flask-shape being characteristic. Average size 3 to 7 μ by 2 to 6 μ . Grows freely on maltose agar at 25°, peptone broth with 1% oleic acid and 1% glucose added. It is almost universally present in the human scalp and has been cultivated by W. G. Garner since 1908.

For details of **Acne Vaccine** *vide Vol. I, p. 901*.

Actinomycosis. A parasitic disease, due to the "ray fungus," first observed in cattle (wooden tongue), characterised by chronic inflammation, with or without suppuration, frequently resulting in formation of granulation tumours, especially about the jaws.

To identify the fungus. 1. Place specimen, pus or sputum, in a flat glass dish on a black surface. Remove the characteristic yellowish particles if found, and carefully tease out on a microslide or cover-glass. 2. Fix film over the flame. **Stain by the Gram-Eosin method:** Cover the film with alcohol for $\frac{1}{2}$ minute,

then for 10 minutes with aniline gentian violet (1 part of concentrated alcoholic gentian violet and 9 parts of saturated aqueous aniline). Stain with Gram's iodine solution (iodine, 1 g.; potassium iodide, 2 g.; water, 300 ml.) for 3 minutes, decolourise in alcohol, wash in water and counterstain with eosin (5% aqueous solution).

The violet-stained mycelium of the fungus, will be seen as tangled webs or scattered branching filaments, on a pink ground (leucocytes, epithelia, etc.), with a $\frac{1}{8}$ -inch or even $\frac{2}{3}$ -inch objective.

The "rays" may be observed without staining, but the stained specimens are confirmatory and are valuable for reference.

While in some text-books actinomycosis is supposed to be caused by two different organisms, *Actinomyces hominis* and *A. bovis*, the former an acid-fast, aerobic streptothrix commonly found in grasses, and the latter a non-acid-fast anaerobic streptothrix which has not been found outside man or animals, modern workers ascribe the disease solely to the latter, which was found in 29 consecutive cases seen in the London Hospital over 5½ years. *A. bovis* has been found in the tonsils of healthy persons and in carious teeth, and the view is now held that infection takes place from organisms in the alimentary tract. The infection may be initiated by injury produced by foreign bodies (e.g. by chewing a straw) but the association of foreign bodies with the disease has been overstressed. *A. bovis* is always associated with other bacteria (e.g., the colon bacillus) and although in many cases the infection appears to be pure it will be found that a minute bacillus, *B. actinomycetum*, is also always present and constitutes the bulk of the gram-negative material observed in sections of the actinomycotic granule, and their constant presence is important in showing how the infection can be initiated.

Clinically, the infections can be divided into two main groups: the superficial group, including the cervico-facial variety and subcutaneous infections of the limbs, and the deep group including the thoracic and abdominal cases. Prognosis depends on the anatomical site of the lesion—if near the surface, allowing ready discharge of its granular and pustular content, the patient recovers, but if deeply placed free drainage is not easily established and the patient may succumb from extension of the disease or from amyloid disease. In cervico-facial cases, before the formation of pus, trismus is the most important sign. Adequate drainage and massive dosage with iodides appear to give best results. Early diagnosis may be made by tilting a test-tube of actinomycotic pus when the granules are visible to the naked eye as greenish-grey specks adhering to the glass. Where cases are allowed to suggest the disease by their chronicity the disease has usually spread beyond human aid.—R. Bates, *Lancet*, i/1933, 571.

True primary actinomycosis is rare; the presence of *B. actinomycetum comitans* is diagnostic. The relationship of this organism to *A. bovis* is not clear. No relationship established between "vegetable trauma" and the disease.—R. Klaber, *Brit. J. Derm.*, 1934, 12.

Primary ovarian actinomycosis. A unique case in which the ovary was the primary seat of infection.—*Lancet*, i/1909, 758.

Actinomycosis of Tongue. In cases seen very early, presenting a firm small nodule in the tongue, excision and primary closure, followed by X-rays (or radium) applied to the tongue, with fairly large doses of potassium iodide internally (30 grains increasing to 90 grains three times daily), practically always results in a permanent cure. When an abscess appears, incision to establish drainage is necessary; the abscess walls should be curetted, the abscess wabbed out daily with half-strength tincture of iodine, and a mouth wash employed three times daily. Röntgen or radium therapy should be begun soon after incision. In one case, lightly-filtered X-rays with from 100 to 125 röntgens weekly for 4 or 5 doses proved sufficient: in another case, 1 dose of 300 röntgens, well filtered, sufficed. If submental abscess nodule formation occurs by extension, daily opening of fluctuant regions and insertion of iodoform gauze drains is necessary, and X-rays should be directed towards the base of the tongue via the submental approach, as well as to the dorsum (cross fire). Copper sulphate stick locally and $\frac{1}{4}$ grain doses by mouth have also been recommended.—O. J. Cameron, *J. Amer. med. Ass.*, ii/1932, 1148.

Actinomycosis, 23 cases. Promoted efficient drainage and curetted with a dry gauze swab. Vaccine therapy employed.—L. Colebrook, *Lancet*, i/1921, 893.

A case of actinomycosis of the lungs.—*Brit. med. J.*, i/1912, 302. Local lesion closely resembles tuberculosis.

Actinomycosis of the cæcum. On opening the abdomen, a quantity of purulent fluid welled up (actinomyces found). Potassium iodide 50 grains thrice daily.—E. G. Slesinger, *Lancet*, i/1920, 1220.

Actinomyces vaccine suggested of strength 1 ml. = 0.0001 g. solid substance as initial dose, rising to 1 ml., containing 0.001 g., repeated according to clinical symptoms.

The mycelial threads can easily be broken up into fragments resembling bacilli, hence the method of counting the component parts may be used to denote the strength of this vaccine. Dose: 3 to 10 millions.

See also *Vol. I*, pp. 706 and 1023 for further details of treatment.

Ankylostomiasis. The worm producing this disease (*Ankylostoma duodenale*) is about $\frac{1}{4}$ inch long and of a whitish colour. Its habitat is the small intestine of man. It attaches itself to the mucous membrane, and no fewer than 1000 of them have been obtained from one patient. The male and female worm are quite different in formation. The eggs pass away from the patient—as many as 8,000,000 have been passed by a sufferer in a single day—and the small thread-worm escapes from the egg. Mines afford an excellent hatching place for the young larvæ. Hygiene and sanitary measures are necessary to stamp out the disease.

LIFE HISTORY detailed, mode of infection, duration of infectivity. There are said to be two causative organisms. The disease in the southern regions of the U.S. and in Porto Rico was thought to be due usually to *Ankylostoma* (*Necator*, *Uncinaria*) *Americanum*, as distinct from the generally known *A. duodenale*. *A. Americanum* has not been identified in the Cornish mines. Where both species are abundant, individuals are often doubly infected. Methods of detecting eggs in fæces, *v. Lancet*, i/1911, p. 783. See also *Brit. med. J.*, ii/1909, 775.

The anæmia caused is frequently profound, producing ultimate death. Milk diet for a day or two, then calomel and saline aperient; the following morning thymol 20 to 30 grains in a cachet, repeated twice at 1 hour's interval, with another saline aperient 2 hours after the last dose.—*Brit. med. J.*, ii/1909, 1350.

For further details on treatment *vide Vol. I*, pp. 421, 610, 800, 848, 873, 1026.

The infection is so serious amongst miners in the mining districts of Rochela-Molière and Firminy, in the basin of the Loire, that special clinics have been established. Thymol preferable to tetrachlorethane or carbon tetrachloride, which is too toxic and uncertain in action.—Garin, Rousset, and Gonthier, *per Brit. med. J.*, i/1933, 702.

Repeated doses of 2 g. of hexylresorcinol gave only 26 cures in 50 cases Egypt.—A. C. Biggam and P. Ghalioungui, *J. trop. Med. (Hyg.)*, 1933, 353.

Hexylresorcinol an inefficient substitute for older anthelmintics in ankylostomiasis, although it appears to be safe.—P. A. Maplestone and A. K. Mukherjee, *Indian med. Gaz.*, 1932, 610.

The cardiac complications of ankylostomiasis.—H. O. Gunewardene, *J. trop. Med. (Hyg.)*, i/1933, 49.

Anthrax. *Bacillus anthracis* was probably the first bacterium to be recognised, inasmuch as it was associated with splenic fever as long ago as 1849. It is responsible for "malignant pustule" in man. If an animal die suspected of the disease the mode of examination is to cut off the ear and submit the blood from the same to bacteriological examination. The organism does not form spore in the body of the animal, but if the air gain access, as in the case of an ordinary post-mortem investigation, the organism forms spores rapidly and hence becomes a grave source of danger.

The organism is non-motile and almost invariably occurs as long filaments, particularly in broth cultures. It grows on all the ordinary media both at room and body temperature, and produces in gelatin "stab" cultures typical "inverted fir trees" appearance. By growing at 42° a non-sporing form can be produced, which is the mode of attenuation for the immunisation of animals, as introduced by Pasteur. The spores retain their vitality and pathogenicity for years in dry conditions. Martin has shown that the organism produces an alkaloid, which is the fever-producer, and an albumose which induces the coma.

Staining of the blood may be conducted by Gram's method (counterstaining with eosin), also by alkaline methylene blue. The organism is gram-positive.

The malignant diseases which the organism produces in man have been satisfactorily treated by **Sclavo's Serum** (*q.v.*) or other anti-anthrax serum or by excision. If not diagnosed in time, the organism may invade the blood stream, causing death, with symptoms of splenic fever, but the spleen is not enlarged nor the bacilli so numerous in the organs.

Changes which occur in growth of the organism.—*Brit. med. J.*, ii/1911, 166.

Safranin, 1 in 5,000, is stated to kill the spores of *B. anthracis* in 30 minutes.—G. Salviola, per *Pharm. J.*, i/1923, 547.

At Bradford Royal Infirmary (pulmonary anthrax is still named "maladie de Bradford" in France) excision has now been replaced in most cases by injection of salvarsan, either alone or combined with Sclavo's serum.—F. W. Eurich, *Brit. med. J.*, ii/1933, 52.

See also Vol. I., pp. 901 and 1026.

Appendicitis. Common intestinal parasites seem to be associated with this disease, e.g., *Ascaris lumbricoides* and *Trichocephalus dispar*. Chauvel has pointed out that appendicitis appears to be most prevalent among meat-eaters, and notably beef-eaters. It is, on the other hand, unknown amongst Arabs or the Chinese. In religious communities in Brittany, where meat is never eaten, appendicitis is unknown.

Disease of the vermiform appendix may be initiated more frequently than commonly supposed, by entozoa, e.g., *Oxyuris Vermicularis* and *Trichocephalus*. *Trichiurus* may prepare the way for bacterial infection.—*Brit. med. J.*, i/1910, 4.

"Wisp" **Bacillus** found in septic wounds is small, slender, gram-positive, non-motile, and appears in V-shaped bundles something like the diphtheria

group. Grows in the depths of an agar or glucose-agar "shake" or "stab." Obligate anaerobe. In civil practice found in appendix abscess cases or other suppurations from the intestines.—A. Fleming, *Lancet*, ii/1915, 642.

Theories of causation revised. Foreign bodies and trauma very exceptional causes.—A. Krecke, *Münch. med. Wschr.*, 1933, 299.

Discussion on appendicitis, *Proc. R. Soc. Med.*, 1932, 181.

Diagnosis. Atropine, 1/100 grain *per os* or subcutaneously, followed in half hour by large enema; if tenderness still persists over appendix, positive diagnosis should be made.—F. M. Findlay, *New Engl. J. Med.*, March 1933, 630.

Beri-beri. A form of polyneuritis. Endemic in the Federated Malay States and parts of China.

Two well-marked forms of beri-beri are recognised. The "dry type" is characterised by muscular wasting, anæsthesia of the skin, and paralysis of the muscles of the legs, arms and chest, with degeneration of peripheral nerves, while the most characteristic symptom of the "wet type" is œdema of the limbs and trunk, with effusion of fluid into serous cavities.

Aetiology. Eykman first brought forward (1897) evidence to establish a close connection between polished rice and the incidence of beri-beri. The characteristics in man, which arise from degeneration of peripheral nerves (polyneuritis), have their counterpart in birds fed on milled rice. Feeding the latter with rice bran revives them.

"Overmilled" would perhaps be a better term than "polished" rice. Rice thus "polished" is deprived of pericarp, subpericarpal layers and embryo or germ. Beri-beri does not occur in races using partly milled "cured" rice, and the poorly nourished are more liable to contract it than the well fed.

The researches of recent years have not shaken the established fact that human beri-beri is primarily due to deficiency of the antineuritic factor. On the other hand it is probably unwise to regard the beri-beri problem in the tropics as being solely a question of polished or unpolished rice. The work of McCarrison (*Indian med. Res. Mem. No. 10*, 1928) suggests that human beri-beri may occur in spite of the presence of a certain amount of vitamin B₁ in the diet. Clear and convincing evidence has nevertheless accumulated that the substitution of undermilled for milled rice will cause beri-beri to disappear.—*Vitamins*, Medical Research Council, 1932.

B. asthenogenes, an aerobic saprophyte, capable of living anaerobically, when cultivated on polished rice, produces free acid up to 1%; if the acid produced is continually neutralised, 22% can be obtained, chiefly of propionic acid. The effect of *B. asthenogenes* infection, in young pigs fed on polished rice, is to cause ulceration of the stomach due to propionic acid. Results of fermentation profoundly modified if husks and rice are mixed in equal proportions, or if large amounts of protein food are present. These facts should be considered with reference to beri-beri among human rice-eaters.—"Research on Beri-beri," P. Noel Bernard and J. Guillermin, *J. trop. Med. (Hyg.)*, 1924, 82.

B. asthenogenes exists in two forms: aerobic and saprophytic in presence of vitamin B; anaerobic and pathogenic in absence of vitamin B. It is suggested that it is the vitamin deficiency which renders the body very liable to infection by the bacteria.—A. Cannon, *Brit. med. J.*, ii/1929, 853.

Deficient diet, merely a predisposing factor, the **Bacillus beri-beri** being the principal aetiological factor. *B. beri-beri* is a gram-negative, motile organism and does not form spores. It has peritrichal flagella. It does not liquefy gelatin; it

produces indole, coagulates milk, and shows a distinctive colony on agar plate. It ferments the common hexoses, also maltose, lactose, saccharose, xylose, the hexatomic alcohols, mannitol and sorbitol, and glycerin, rhamnose and arabinose with production of gas and acid. Resembles *B. coli communior* but is differentiated by the fact that it agglutinates and gives a complement fixation reaction. The serum from experimentally infected animals and from human case contains potent specific agglutinins for the *B. beri-beri*. Of the fæces of 135 cases 98 showed presence of *B. beri-beri*; the incidence of the bacillus among persons without beri-beri was found to be about 1%, which is about the percentage of carriers of intestinal pathogenic bacteria in general. As a result of agglutination tests on 30 consecutive beri-beri patients 25 were positive, while with 40 controls only 3 were positive.—S. Matsumura and co-workers, *J. Amer. med. Ass.*, i/1929 1326.

Treatment.—The number of clear-cut clinical experiments on record in which adult beri-beri was treated by vitamin B₁ alone, without other dietary alteration, is not large. Failure to secure obvious benefit by means of vitamin B extracts may be due to too small a dosage. While stress should be laid on vitamin B₁ in treatment, it is reasonable to give in addition a good all round diet containing abundant proteins, vitamins and mineral salts.—*Vitamins*, Medical Research Council, 1932.

Phaseolus Radiatus. The fruits called by the Malays Katjany-idgo bean have been used in beri-beri. The beans when used by addition to rice have an unpleasant flavour. They are boiled into a porridge with the rice in the proportion of $\frac{1}{8}$ pound of beans to $1\frac{1}{8}$ pounds of rice. The rice should, if possible, be freshly husked daily.

In the Philippines a preparation of rice polishings called **Tiqui-Tiqui** is stated to be efficacious for children.

The anti-beri-beri vitamin occurs in the aleurone layer of the grain beneath the husk and in the germ of the grain. British flour owing to its excessive refinement, involving the almost complete removal of the aleurone layer with the husk, and also of the germ, is not protective against beri-beri. "**Atta**," Indian flour contains the aleurone layer and the wheat germ—this is protective against beri-beri.

For further information on the vitamin B complex see p. 379.

Blackwater Fever. *Syn.* MELANURIC FEVER.

Severe rigors generally at onset, bilious vomiting, and hæmoglobinuria. Generally thought to be a form of malaria, but Manson places it by itself pending settlement. The analogy between this and the hæmoglobinuric fevers of cattle is striking.

Aetiology. Blackwater fever is not a disease *per se* but only a complication of a severe infection of malaria, which is made premature by the exhibition of a dose of quinine larger than that usually taken. The action of the quinine on the large number of severely poisoned cells accounts for the explosive character of blackwater fever. It should be called "Malarial hæmoglobinuria." Many cases of malaria occur with blackwater fever, but no blackwater fever ever occurred in W. Africa without previous malaria. Malarial parasites can be found in more than half the cases both before and after the attacks. The presence of polychromatocytes (erythrocytes occurring in certain malarial bloods which have the characteristic of a peculiar bluish staining known as the condition of polychromiasia or polychromatophilia) is of great diagnostic value as to the presence of obscure malaria. For the production of the symptom or complication of blackwater in Europeans it is not so much the question of the number of parasites, but of the amount of toxin set free, which, together with the poisonous effect of the quinine on the polychromatocytes

thus made, produces a quantity of hæmoglobin in excess of what the body can deal with. This would explain why the intensity of blackwater fever varies, since it *must vary directly with the amount and virulence of toxin operating, and, to a less extent, directly with the amount of quinine.*

Prophylactic quinine must be used scientifically. 5 grains is not necessarily a prophylactic dose, though it is a useful average, and a man with an attack of fever while taking this dose will only have a very mild attack. Any factor *which impairs the body's efficiency* may turn a not too severe attack of malaria into one of malarial hæmoglobinuria.—W. A. Young, *J. trop. Med. (Hyg.)*, 1923, 350.

Malaria parasites found on the day before onset in about 75% of cases; on the day of onset, in 50%; and on the day after onset, in about 20%. That quinine can produce hæmoglobinuria is certain—two cases quoted.—J. W. W. Stephens, *Int. Conf. trop. Amer.*, 1924, 123.

Hæmoglobinuric fever caused only by repeated and intense infections with pernicious malaria over prolonged periods and in the author's opinion the only parasite concerned as the true causal factor is *P. falciparum* (*syn. Laverania malariae*)—morphology.—J. G. Thomson, *Int. Conf. trop. Amer.*, 1924, 130. W. M. James thought there were few, if any, to-day who hold that blackwater fever is a clinical entity unconnected with malaria. He agreed with Thomson as to *P. falciparum* being the causal factor. The proportion of parasites on blood examination was remarkably constant, being 80% *P. falciparum*, 24% *P. vivax* and 1% *P. malaria*.—*ibid.*, 136, 139.

As far as Southern Rhodesia is concerned, the relationship between malaria and blackwater fever may be regarded as established; it is a manifestation of infection with malignant tertian malaria. The popular belief held in Rhodesia that quinine is an excitant of blackwater has not been disproved and in some cases the connection seems almost impossible to escape. No treatment yet devised has special claim to attention.—G. R. Ross, per *Lancet*, ii/1932, 636.

Technique of Blanchard and Lefrou for the discovery of pseudo-spirochætes in hæmoglobinuric fever. 10 ml. of blood is drawn from a vein into a centrifuge tube containing 1 ml. 20% sterile sodium citrate solution; this is shaken up to prevent clotting and is then centrifuged three times. After the first centrifuge of 10 minutes the corpuscles are thrown down, leaving the citrated plasma above. The supernatant plasma is drawn off into a second sterile tube and centrifuged for another 10 minutes, until there is a slight red deposit consisting of red cells, leucocytes and blood platelets. The supernatant fluid is decanted into a third tube and centrifuged for 20 to 30 minutes, till a white deposit is seen—this contains the spirochætes.—J. G. Thomson, *J. Trop. med. (Hyg.)*, 1923, 252.

The workers above referred to discovered a parasite *S. bilihæmoglobinurie* in the blood, which they assign as a cause. Prof. Blacklock of the Liverpool School Lab., Sierra Leone, injected into a healthy adult the blood of a patient suffering from the fever. The temperature of the patient at the time was 102.5°F. No ill-effects after 6 months. The evidence is against a spirochætal or other specific organismal origin.—*Brit. med. J.*, i/1923, 1030. See also *Lancet*, ii/1923, 1362; W. M. Hewetson, *J. trop. Med. (Hyg.)*, 1924, 333; G. C. Low, *Trans. R. Soc. trop. Med. Hyg.*, 1923, 201.

A critical review of work on the pathology of blackwater fever, with special references to hæmoglobinuria and the conditions in which jaundice has been observed.—Prof. W. Yorke, *Trop. Dis. Bull.*, 1922, 631.

Recent research in blackwater fever.—N. H. Fairley and R. J. Bromfield, per *Brit. med. J.*, ii/1934, 1154.

Treatment. The ordinary antipyretics should not be used; sponging is generally sufficient.

Caffeine sodium benzoate intravenously twice daily, morning and afternoon, accompanied by large quantities of saline water hypodermically or intravenously.—A. A. Facio, *Int. Conf. trop. Amer.*, 1924, 144.

Plenty of fluid the essential basis of treatment. No evidence to support the view that intravenous alkalis or blood transfusion are advisable—the facts indicate that they are actually dangerous in some cases. There has been no improvement in therapy for the last 20 years.—Warrington Yorke, *Brit. med. J.* ii/1932, 838.

Malaria with blackwater fever complications should be treated with quinidine and Atebrin instead of quinine.—R. Knowles and B. M. Das Gupta, *Indian med. Gaz.*, 1932, 432.

Blastomycosis.—Excluding coccidiosis (a disease practically occurring only in males who have lived in the San Joaquin Valley, California, and almost invariably fatal), the unsatisfactory term “blastomycosis” connotes infection with true yeasts, with *Torula* and with oidiums. From the clinical point of view, the three infections are not readily distinguished, but oidiomycosis is a less rare disease than the others and exhibits itself either as a chronic skin disease with miliary epidermic abscesses or as a general or brain infection with fever and leucocytosis, the skin and all the organs being affected. The condition is usually improved by administration of iodides. The term “blastomycosis” signifies no more than a disease caused by a budding organism and should be discarded—*Torula Infection in Man*, Stoddard and Cutler, *Monogr. Rockefeller Inst. med. Res.*, No. 6, 1917, reviewed *Brit. med. J.*, i/1917, 460.

Coccidioides, or “Californian disease,” closely resembles blastomycosis. A causal factor is mould, probably belonging to the group of oïdia. May be primarily cutaneous and often gives rise to generalised lesions with abscess formation; frequently affects the lungs and closely simulates pulmonary tuberculosis. Prognosis very grave in acute cases, with fatal issue in less than six months. Colloidal copper intramuscularly, reinforced by coccidioidin, is a valuable treatment.—Review of “Fungous Diseases,” by H. P. Jacobson (Baillière Tindall and Cox), *Brit. med. J.*, i/1934, 19.

Coccidia and coccidiosis of domesticated game and laboratory animals, and man.—E. R. Becker (Iowa: Collegiate Press, Inc., 1934); review, *Lancet*, ii/1934, 362.

Botulism

Food Poisoning (Bacterial). By virtue of Section 7 of the London County Council (General Powers) Act, which received Royal assent in July 1932, **food poisoning is now a compulsorily notifiable disease in London.** A registered medical practitioner who suspects or becomes aware that a patient is suffering from food poisoning must forthwith notify the district Medical Officer of Health on a certificate stating: (a) the patient's full name, age and sex; (b) postal address of the house or premises where the patient is; (c) particulars of the food poisoning; (d) a statement whether the case is in the notifying practitioner's private practice or in his practice as Medical Officer of a public body or institution. Failure to notify involves liability to a penalty not exceeding 40s.—*Lancet*, ii/1932, 745.

Savage divides food poisoning outbreaks of bacterial origin—chiefly caused by flesh foods—into three classes. (1) Those due to Gaertner group bacilli—the great majority of the large outbreaks. (2) Cases of botulism—a small group due to *B. botulinum*. (3) Those due to toxic action of other bacteria, usually stated

be putrefactive bacteria, such as *B. coli* or *B. proteus*, but there is no clear evidence on this point.

Gaertner Group Bacilli. The Gaertner (or *Salmonella*) group is fairly distinctive and intermediate between *B. typhosus* and *B. coli* in the colon-typhoid group of bacteria, and is frequently called the Paratyphoid-Enteritidis group. They possess the following characteristics: short sporeless bacilli with rounded ends, motile, gram-negative, grow on gelatin with white or translucent growth without liquefaction. Pathogenic members of this group, including *B. enteritidis*, *B. paratyphosus* B, *B. suis-pestifer*, have the property of producing in the animal body toxins which are remarkably heat-resisting. This accounts for numerous poisoning outbreaks in which no living Gaertner organisms were found—sterilisation killing the bacteria but leaving the toxins unchanged.

Differentiation of Food-poisoning Bacteria.—The sodium salts of citric, *d*-tartaric, *l*-tartaric, *m*-tartaric, fumaric and mucic acids are useful in differentiating the Salmonellas. The organisms vary in their power to decompose the sodium salts; all the acids mentioned yield insoluble lead salts, and by these two factors the members of the group can be differentiated with the exception of *B. enteritidis* Gaertner which is variable.—H. C. Brown and co-workers, *Lancet*, i/1926, 117; see also *J. Hyg., Camb.*, Oct. 15, 1924.

Investigation of the Salmonella group, with special reference to food poisoning. The name includes the *B. enteritidis* of Gaertner, the paratyphoid A and B, *B. ærtrycke* (4 types), and *B. suispestifer* (including *B. paratyphosus* C and the hog cholera type), and *B. abortus equi*.—*Brit. med. J.*, i/1925, 373. See also *Lancet*, ii/1926, 397.

The use of certain carbohydrates and glucosides to distinguish members of the Salmonella group of food-poisoning bacilli.—F. Wokes and J. H. Irwin, *Quart. J., Pharm.*, 1927, 514; *Pharm. J.*, i/1927, 747; *Chem. & Drugg.*, ii/1927, 37.

Identification of Salmonella types. Some technical hints from the Pathological Laboratory of the Ministry of Health on the isolation and identification of Salmonella types.—*Rep. med. Offr Minist. Hlth, Lond.*, 1933, 189.

Three cases of acute poisoning (one fatal) due to eating ducks' eggs infected with *B. ærtrycke*. Eighteen birds out of one flock of 46 proved to be infected and 4 laid infected eggs; all 9 in another flock were infected; and 2 out of 5 in third. Birds surviving infection evidently become chronic ovarian carriers and lay sporadically infected eggs.—*Lancet*, ii/1932, 357.

Reports of 19 outbreaks of food poisoning in the Ruhr district of Germany due, apparently, to ducks' eggs. Ninety-nine persons affected, with 4 deaths. Imported eggs from Holland were responsible for most of the outbreaks, infection apparently being very common in duck establishments in Holland, where sometimes as many as 80% of the young ducks are stated to have died of epidemic disease.—W. Fromme, per *Brit. med. J.*, ii/1934, 1002. See also paratyphoid fever, this volume.

B. botulinus is a large bacillus (4 to 9 μ by 0.9 to 1.2 μ), which sometimes forms short threads. It is an obligate anaerobe, slightly motile, with four to eight flagella. The optimum temperature of growth is 20° to 30°—spores are not formed at 37°. It is gram-positive, but does not hold the stain strongly. The bacillus will not grow to any extent in the animal body, poisonous effect being produced by toxins excreted into nutrient material. The toxins—unlike those from the Gaertner group—are destroyed by efficient cooking. *B. botulinus* will not grow in media containing more than 6% sodium chloride, so that, salting, a 10% solution of brine should be used.—From "Food Poisoning" by W. G. Savage. *B. botulinus* spores are highly resistant to heat.—*Yearly Pharm.*, 1919, 39.

The bacteriological diagnosis of botulism.—*Brit. med. J. Epit.*, i/1926, 36.

Occurrence. In 624 samples of soil, vegetables, fruit, feeding-stuffs, etc. collected in California, the bacillus was found in about 30%, and, contrary to common assumption, more abundantly in virgin mountain and forest soils than in cultivated places. The bacillus seems to be a common soil anaerobe, but conditions under which it causes toxic symptoms in man have not been defined.—*Nature, Lond.*, i/1923, 95.

Canned Food Poisoning. Tins passed as sound often contain living micro-organisms in a dormant state, becoming unsound when conditions favour vegetation of spores of proteolytic or fermentative micro-organisms. Specific bacteria associated with outbreaks of food-poisoning are confined to the Salmonella group (*B. enteritidis* Gaertner and *B. ærtrycke*) and the *B. botulinus*, which are rarely found in canned foods imported into the U.K. The Salmonella group has been responsible for 51 outbreaks of food-poisoning in the U.K. since 1882, 17 of which were due to the living bacilli and 27 due to undestroyed toxins formed before canning; 26 were caused by canned meats. In 10 out of 14 outbreaks during 1919 to 1922 the tins came from S. America, which supplies 53.5% of canned meats imported by the U.K. 16 of the remaining outbreaks due to this group were due to salmon (infected with living bacilli, survivals from infection at place of canning), and 9 to other fish, crustacea or fruit. In the case of fish, the contents of the tins undergo, in time, maturation changes, which are considered beneficial rather than otherwise. Botulism is common in the U.S. and Canada—84 outbreaks between 1906—20, comprising 319 cases with 206 deaths, all traced to tins of canned fruit or vegetables. Canning does not kill the spores in the fruit already present. The spores, if scanty, will not produce sufficient changes to cause rejection of tins as unsound but will cause tins to be "blown" and contents to have offensive odour; non-vegetating spores of bacillus not injurious. Most tins of condensed milk are imported from the U.S.—no sound tins of sweetened milk found to be sterile.—"Canned Foods in Relation to Health" by W. G. Savage and R. F. Hunwicke, *Brit. med. J.*, i/1924, 127.

Sporing aerobic bacilli are frequent in sound canned foods, but are unable to develop and remain as harmless spores. Obligate anaerobic bacilli are rarely present in sound tins, but were nearly always associated with obtrusively decomposed conditions in the tin. Nearly 62% of sound tins are not sterile, the worst offenders being those containing crab and lobster.—"Food Invest. Spec. Report," No. 11, *Nature, Lond.*, ii/1922, 614.

Home-canning methods responsible for recent small outbreaks. Sterilisation under pressure is the only method recommended. For such vegetables as peas, corn, string beans, spinach, asparagus, and root vegetables, and for meats, the various boiling water methods are very unsafe and should not be used.—*J. Am. med. Ass.*, ii/1928, 730.

Loch Maree Hotel food poisoning tragedy (1922). Eight persons lost their lives through eating wild-duck paste. The shortest incubation period was 14 hours and the longest 43 hours. *B. botulinus* and its toxin were found in one of the pots of paste.—T. K. Monro and W. W. N. Knox, *Brit. med. J.*, i/1922, 279.

The **symptoms of botulism** are very characteristic, and strikingly different from those met with in ordinary food-poisoning cases. They are almost entirely referable to lesions of the central nervous system. Prominent symptoms are those due to disturbance of digestive tract—thirst, feeling of constriction in the throat, dysphagia, obstinate constipation and ocular symptoms. Symptoms usually appear 12 to 24 hours after eating the infected food.

For further information re Botulism, see Vol. I., p. 1034. For Putrefactive Bases (Ptomaines) see this vol., p. 467.

Cancer. The virus theory. W. E. Gye and J. E. Barnard, working under the auspices of the Medical Research Council, claimed to have discovered the causal organism of malignant growths. According to these workers there are two factors concerned in the aetiology of cancer: (1) a living virus—the extrinsic factor, and (2) a chemical substance produced by the cells—the intrinsic factor. The causal organism apparently is “in the air,” but it does not appear to affect normal, healthy tissues. Long and complete papers by these workers were printed in the *Lancet*, ii/1925, 109, 117.

A review of work leading up to Gye and Barnard's researches.—*Lancet*, ii/1925, 135. See also *ibid.*, 302, 408.

Discussion on filter-passing viruses and cancer.—*Brit. med. J.*, ii/1925, 189-195.

GYE fails to state whether or not cultures derived from rat and mouse tumours will, on addition of the specific factor, produce likewise tumours in mice and rats, though such positive result is needed. It would be necessary not only to propagate the parasite but also to prepare a culture, and through inoculation from the culture to secure further cultures from which tumours are produced. Gye's results are impaired in that the so-called chicken sarcomas are usually regarded as different from the sarcomas of man and as merely infective granulomas; in any case they are biologically, of all animal tumours, the furthest removed from human cancer. Gye's results are of paramount importance for the rôle of a virus or a group of viruses in the pathology of tumours, though all his conclusions are not justified. As several workers have obtained 100% positive results in cancer formation by applying irritants, one cannot ascribe the inorganic production of cancer by tar, etc., to a parasite (the irritant causing tissue changes and preparing the way for infection by the virus, which then penetrates the cell and propagates), unless one arrives at the improbable conclusion that the virus is ubiquitous. It is possible, however, that the bacteria outside and inside the tumours are laden with a virus which is further cultivated with the propagation of the bacteria, and it is probable that other organisms may take up the virus, in which case various parasites might acquire carcinogenic properties. What Gye failed to accomplish—production of cancer-like tumours in rats and mice with a virus derived from human cancer—BLUMENTHAL did with his bacteria; the bacilli themselves were not demonstrated in the tumour, but were found in the droplets resulting from liquefaction of the tumour. It would be a further advance if it could be shown that the cancer-producing properties of these parasites were due to a virus or group of viruses, and although Gye and Barnard have not succeeded in this demonstration, their researches constitute an important step. Gye's discovery that the virus has to be cultivated anaerobically is of special interest and is in agreement with the findings of other workers, i.e., that cancer cells are anaerobic, in contradistinction to normal cells. Gye's experimental results are in harmony with the findings reached in other ways and although his researches do not furnish an unequivocal solution of the origin of cancer, they give a stimulus to research.—Prof. Blumenthal, *Dtsch. med. Wschr.*, per *Amer. med. Ass.*, ii/1926, 625.

The virulence of a filtrate of chicken sarcoma can be increased or diminished by addition of a variable quantity of an acid salt, the **mono-potassium phosphate**. Gye neglected this factor, never having controlled it, but each time he was able to show activation of virus acidity was increased, whilst non-active control injections were always in neutral or slightly alkaline solutions. Neither his two factors, nor his supposed “cultures” of the virus of neoplasma, necessary or proven.—E. Harde, *J. trop. Med. (Hyg.)*, 1926, 159-161.

Gye's work leads to the conclusion that the entrance into a normal cell of specific virus confers on the cell characteristics which are the essential features of malignancy; this virus is apparently the same for many different classes of animals; alone it is unable to effect entrance into a normal cell, but requires an accessory biological factor—in the case of the Rous tumours a chemical substance furnished by the tumour cells; it is not essential that the cells of every neoplasm must produce such a substance—it is sufficient for

the virus to be able to enter a few cells. The cells of the Rous tumour are exceptional in forming an abundance of this specific factor; further work will have to show whether different sarcomata vary in the amount of stability of the specific factor formed by them. *The virus by itself is non-pathogenic which explains why the disease is non-contagious.* Gye's work has solved our old and fundamental difficulties—it does not compete with any previously established facts, but confirms them; it is the first adequate explanation of the causation and growth of cancer.—W. Cramer, *Brit. med. J.*, i/1926, 175-180.

Effects of antiseptics on Rous tumour extracts. Chloroform, phenol, sublimate, toluene, ether, hydrogen peroxide, formalin, acriflavine, and hydrocyanic acid have been tested and found effective in abolishing the activity of the extracts. Chloroform acts very rapidly, acriflavine slowly. There is, however, an agent contained in tumours of diverse origin and of diverse structure which can reactivate an extract which has been inactivated by an antiseptic. This agent is a living filtrable microbe and is the cause of new growths.—W. E. Gye, *Brit. med. J.*, ii/1926, 865, see also *ibid.*, 897.

Experiments confirming the presence in Rous sarcoma fluid of two causative factors which, individually inert, in combination give rise to tumour growth. Other points digressing from Gye's work.—R. D. Mackenzie and C. F. Villingworth, *Lancet*, ii/1926, 745.

In a report on Cancer Research in the U.S., Dr. A. Leitch said that American workers had in the main failed to agree with the Gye theory—and it was evident that here at home scientists as a whole had failed to accept it as conclusive.—*Brit. med. J.*, ii/1927, 112.

The real nature of the cancer agent seemed at least to be emerging. The indications were that one had to deal with an endogenous chemical substance rather than with extrinsic living viruses. The parasitic theory of cancer formation considered highly improbable.—J. B. Murphy (New York). If a virus were so small that it could live and multiply in the interior cells it was well situated for influencing such cells. The virus theory had been regarded too lightly.—J. McIntosh, *Int. Conf. on Cancer*, London, July 1928, *Brit. med. J.*, 105-109, 165-173.

The **Young-Glover micro-organism** (a pleomorphic micro-organism isolated simultaneously but independently by Young, in Glasgow, and Glover, in Toronto) is a microbe which, while possessing as alternative phases coccal, bacillary, yeast, and hyphal forms, lives ordinarily in the cancerous tissue as a dispersed element so minute as to be invisible. Loudon and McCormack claim to have confirmed that this micro-organism is identical with the filterable virus of Gye and Barnard and M. J. Scott claims to have isolated the Young-Glover microbe and to have produced malignant epithelial tumours in lower animals (monkeys) at the point of inoculation; he also claims to have cured a considerable number of cases (case reports of two are given) of cancer with a serum obtained from young horses immunised against an antigen prepared from the Young-Glover microbe.—James Young, *Brit. med. J.*, i/1926, 67.

Two completely independent factors underlie the change of a normal cell into a cancer cell (1) an antecedent cell susceptibility, often acquired as a result of chronic irritation, (2) the carcinogenic factor (parasite). Evidence obtained that the parasite lives in symbiosis with cancer cell in amorphous phase, and other phases are derived from this during incubation of a cancerous growth. Morphological features resemble life story for other classes of pathogenic organisms; belongs to familiar bacteria widespread in nature. The small proportion of men and animals developing cancer, in spite of the universal exposure, suggests all-importance of cell susceptibility and explains difficulty of producing cancer experimentally by injection of the organism.—James Young, *Brit. med. J.*, i/1925, 64.

RELATION OF CARCINOMA TO INFECTION. Several cases of human carcinoma recorded in which definite local and general reactions occurred after inoculation with vaccine prepared from **diphtheroid bacillus**. Preparation of medium and technique for inoculation and examination of media described.—W. M. Ford Robertson, *Lancet*, ii/1923, 330.

Cancer thought to be caused by **anaerobic bacilli**—such organisms (rarely observed by direct examination of epitheliomata).—Ford Robertson, *Brit. med. J.*, ii/1921, 199. See also W. McAdam Eccles, *Brit. med. J.*, ii/1921, 195.

Irritants in Relation to Cancer

Arsenic Cancer. Arsenic may well be one of many predisposing causes. A case described of a woman who had psoriasis treated by arsenic and who ultimately died of cancer, also a table of numerous allied cases.—*Lancet*, ii/1913, 210, 284. See also Sir J. Bland Sutton, *Brit. med. J.*, ii/1916, 788.

An investigation into the presence of **copper** in tumours and normal tissue, carried out in great detail, showed its presence in over 100 specimens with only one exception. Practically all the internal organs were examined, and considerably increased amounts of copper were found in degenerated tissues, as much as 501 mg. per kilo being present in a carcinoma of the rectum. Suggested that this increase shows that degeneration is associated with an increased catalytic action due to increased amount of copper, or that copper, like calcium, tends to be deposited in degenerated areas.—C. P. White, *Lancet*, ii/1921, 701.

Chemical irritants, sulphurous and sulphuric acids, have also been held responsible for cancer.

Sulphur content in fuel in relation to cancer. Peat is found to be stronger in sulphur in some places than in others and it appears cancer mortality is connected with high sulphur content.—*Lancet*, ii/1913, 506.

Paraffin cancer and its experimental production. By analogy with these results on mice it takes at least 10 years of exposure to paraffin oils to produce cancer in man—agreeing with actual experience.—A. Leitch, *Brit. med. J.*, ii/1922, 1104. See also Soot Cancer, *ibid.*, p. 1113 and Arsenic Cancer, *ibid.*, p. 1107. The theory of irritation hence becomes more impressive.—*ibid.*, 1130.

The cancer incidence among paraffin workers in the Scottish Shale Oil Industry is 0.1% per annum. The condition occurs in workmen about, or over, middle life, who have been paraffin workers for long periods—20 years or more.—Report of Imperial Cancer Research Fund, *Lancet*, ii/1923, 1371.

Liquid paraffin is harmless and not likely to have any of the evils of pitch and tar in causing pitch cancer.—H. C. Ross and J. W. Cropper, *Brit. med. J.*, ii/1913, 48. It is one of the later products of distillation of crude petroleum and is therefore probably quite free from “auxetics” which have been found in the “interim oil scales” produced at oil works in Scotland.—*Brit. med. J.*, i/1915, 445, 530.

Mule-spinner's cancer and mineral oils, and a note on chimney-sweeps' cancer.—A. Leitch, *Brit. med. J.*, ii/1924, 941.

Cancer of the scrotum is sufficiently common among a certain class of cotton-spinners as to be known as “mule-spinners' disease.” Said to be due to the scrotum coming in contact with a part of the machine coated with lubricating oil, which impregnates the spinner's pants.—*Brit. med. J.*, i/1924, 679. It also occurs among sweeps, and tar and paraffin workers.—A. H. Southam and S. R. Wilson, *Brit. med. J.*, ii/1922, 971.

Enormous preponderance of cancer incidence amongst cotton operatives. Mule-spinner's disease one of the most favourable types of malignant disease as it can be detected early and cured by radical removal. Cancer produced in mice with the lubricating oil actually used in cotton mills—shale oil more liable to produce cancer than shale-free petroleum oil, and lubricating oil made from sperm oil is quite harmless. Samples of toxic oils treated with sulphuric acid rendered quite harmless.—*Brit. med. J.*, ii/1928, 68.

A committee of the British Empire Cancer Campaign recommends that owners of mills should mix into their lubricating oil the necessary quantity of sperm oil or lanolin, and preferably use mineral oil as far as practicable saturated.—*Lancet*, ii/1931, 207.

The following suggestions are made to those interested in mineral oil and tar dermatitis and cancer:—(1) Take special precautions with textile grade oils; (2) select well-hydrogenated oils; (3) oils should be subjected to the Edeleanu process (treatment with sulphur dioxide); (4) select oil with a low refractive index; (5) use lanolin-olive-oil protective ointment before work and after the evening bath. If these recommendations are correctly followed, mule-spinner's cancer and allied conditions should become curiosities.—C. C. Twort and J. M. Twort, *Lancet*, i/1934, 286.

Betel-chewing and cancer.—*Brit. med. J.*, ii/1923, 632, 680, 733.

Though betel-nut chewers in India have been proved to suffer from buccal cancer as a result of the habit, the disease in Formosa is comparatively rare though the natives are equally addicted to betel-chewing. Can this be

attributable to a racial immunity or to an unknown factor operative in India and not in China?—*Brit. med. J.*, i/1924, 729.

The older physicians were probably correct when they said that cancer of the mouth would probably disappear if tobacco, bad teeth and syphilis could be eliminated. It seemed clear that cancer only arose on tissue altered by chronic irritation.—James Ewing (New York), Int. Conf. on Cancer, London, July 1928, *Brit. med. J.*, ii/1928, 105-109, 165-173.

Tar Cancer. There are grounds for believing that in human cancer, the antecedents of which are, for the present, hidden from us, some irritant may have been in action and have disappeared, leaving no evidence of its presence, long before cancer declared itself. Remarkable differences in toxic action and tumour-producing powers of tars. Some experiments of Murray suggest that the occurrence of one form of cancer in an individual protects the body in some way against the occurrence of another. Age in itself is not an important factor. It is a question as to the time the causal agent has been in operation. If we expose a child of 10 and an adult of 40 to the same carcinogenic agent and the latent period necessary is 10 years, the cancer would declare itself at 20 in the former and at 50 in the latter.—A. Leitch, *Brit. med. J.*, ii/1923, 1. See also *Lancet*, ii/1923, 1369.

Behaviour of coal tar in the tissues.—L. H. Jorstad, *J. Cancer Res.*, per *J. Amer. med. Ass.*, ii/1925, 852.

The Cancer-producing Factor in Tar. Industrial evidence alone shows that the cancer-producing substance is present in the higher boiling fractions of tar, creosote oil, anthracene oil (and hence in green oil and anthracene) and pitch. Experimental evidence further shows that the substance is not concentrated in the solids suspended in anthracene oil and that it is present in the highest boiling distillate obtainable from pitch. Hence it may distil over through an interval of temperature from 250° (the creosote fraction) to over 500° (the "pitch distillate")—a range of 250° or more.—E. L. Kennaway, *Brit. med. J.*, i/1924, 564.

Nine products tested for production of cancer after heating them to temperatures stated: (1) acetylene 700°; (2) acetylene 800° to 900°; (3) Californian petroleum 880°; (4) isoprene 700°; (5) (6) and (7) Durham Holmside coal 450°, 560° and 1,250°; (8) human skin 920°; (9) yeast 920°. The tarry products were applied twice weekly to mice (generally 100 for each test) in the interscapular region. It is not correct to call these pyrogenous materials cancer producers simply because they are irritants. The irritation must be of a special kind, or must act on some special elements in the tissues. Cancer was produced by the above procedure by substances obtained by heating **acetylene, isoprene, yeast and human skin to temperatures ranging from 700° to 920°**. Acetylene is the simplest organic compound from which a carcinogenic material has been so far obtained. The Californian petroleum which produced no tumours of any kind in mice, in the unheated state, showed active cancer-producing properties after exposure to a temperature of 880°. The cancer-producing substance present in coal tar is found in small amounts below 450°; at 560° it appears in larger quantities, and this increase continues at a slower rate up to 1,250°.—E. L. Kennaway, *Brit. med. J.*, ii/1925, 1.

Prof. B. Bloch, of Zurich, has succeeded in locating the cancer-producing agent of **coal tar** in the **fraction with b.p. over 300°**. It is soluble in benzol. 100% of mice to which it was applied gave rapidly growing carcinomata within 4 months. The hydrocarbons with lower b.p. also produced tumours, but these were benign. It was found that while tumours could be produced in rabbits and mice by applying tar, guinea pigs so far failed to react. This emphasises the susceptibility of the cell as an important factor in genesis of cancer.—*Lancet*, ii/1921, 1235.

It seems that **the particular chemical constituent of tar responsible for the production of cancer is 1 : 2-benzopyrene**, 7 grammes of which can be extracted from 2 tons of gas works pitch. Dibenzanthracene (a synthetic chemical not obtained from tar) has equally powerful carcinogenic properties. It is possible that minute quantities of such substances may be present in food or clothing, or similar substances may be formed as by-products of the body.—*Rep. Brit. Emp. Cancer Campgn*, No. 10, per *Brit. med. J.*, ii/1933, 114.

1 : 2-Benzopyrene, isolated from coal-tar, produced malignant tumours of the skin of mice about twice as rapidly as 1 : 2 : 5 : 6-dibenzanthracene.—J. W. C. Cook, L. Hewitt and I. Hieger, *J. Chem. Soc.*, 1933, 395.

Occupational Cancer. J. C. Bridge and S. A. Henry (Home Office): Cancer, in order to be classified as of industrial origin, must fulfil two conditions: (1) that the incidence rate in that occupation exceeds that of the general population to a significant extent; (2) that in the occupation there is sufficient association of the worker with a substance proved to have carcinogenic properties. There was only one effective method of prevention—substitution of innocuous bodies. A binding substance, non-carcinogenic to animals, had been invented to replace pitch. O. Rostoski and G. Schmorl (Dresden): *Schneeberg lung cancer*, a pulmonary affection due to malignant tumours of the lungs, found in the bismuth, cobalt, and arsenic-mining district in Schneeberg.—Int. Conf. on Cancer, Lond., 1928.

The Lipase Theory. It seems reasonable to conclude that the diminution in lipolytic activity, both in tumours and serum, is due to a real decrease in the production of esterases, though it is not suggested that these enzymes occupy any very unique position in the problem of cancerous growth, beyond the excessive lipid-cholesterol ratio of tumours.—W. C. M. Lewis, *Brit. med. J.*, ii/1926, 923.

The main outcome of researches on lipase since 1911 has been to show that natural and induced tissue lipolysis with the fatty acids or their sodium salts are important factors in the protective processes and resistance of the body in malignant disease.—W. J. Simpson, *Brit. med. J.*, ii/1926, 1080.

It is difficult to avoid the suggestion that the labile chemical substance alluded to by Gye is of a similar nature to inactive lipase, and that it can be activated by its own chloroform-treated filtrate or co-enzyme. Gye notes that the agent or substance, though sensitive to heat, still retains its power in conjunction with the virus to produce a tumour. This brings the inactivated filtrate into line with the heated cancer extracts and filtrates with activating properties on pancreatic inactive lipase.—J. A. Shaw Mackenzie, *Brit. med. J.*, i/1927, 78.

Criticism of Shaw-Mackenzie's views. Does not agree with view of hypercholesterolemia.—A. N. Currie, *Lancet*, ii/1924, 936. Reply, *ibid.*, 1096.

Blood and tissue changes in cancer, with reference to diagnosis and treatment.—J. A. Shaw-Mackenzie, *J. trop. Med.*, (*Hyg.*) Aug. 15, 1925, 297. See also *ibid.*, Dec. 1, 1927.

Cancer a Constitutional Disease. Patients who have previously shown signs of glycosuria later suffer from cancer, or, in other words, glycosurics who have died, have died of cancer. A case of true pancreatic diabetes never known to develop cancer. The metabolic error in glycosuria must be understood to elucidate malignant disease. In glycosuria, sugar appears in the urine in spite of its having been prepared for combustion by insulin, and the reason for its not being burnt is that its final oxidation is only achieved by the simultaneous oxidation of fat. It is obvious, therefore, that the fat cannot have been prepared for oxidation, and hence there must have been a deficiency of lipase. Conversely, in pancreatic diabetes, the fat is ready for complete metabolism, but the sugar is not. The fats of the body, while acting as stores of potential energy are in other ways important cell constituents. They are part and parcel of cell protoplasm. Even in animals killed by starvation, when all the reserve fat is used up, the fats in the organs and tissues remain constant. This "organised" fat, essential to life, is unsaturated and consists largely of phosphatides, in contradistinction to reserve fat which is saturated, and it is important to note that whereas saturated fats are inactive, the more unsaturated they are, the more unstable they become.

The liver contains a relatively large amount of unsaturated fatty acids—in that organ, no doubt, the first stage of fat catabolism occurs. LEATHE'S and MEYER-WEDELL'S rat experiments in 1923 proved that it is the function of the liver to prepare fats in this way, rendering the saturated acids unsaturated.

Neutral fat, when called upon for the needs of the organism, is taken direct to the liver, where it is converted largely into phosphatides, and the fatty acid unsaturated. The phosphoric compounds play an important part in the intermediary catabolism of carbohydrates. The fat is now ready in an unstable form for the repair and maintenance of tissues, in conjunction with carbohydrates which have been prepared by insulin.

The unsaturated fats not only share in the cell structure, but also in the formation of the cell envelope. The pre-cancerous condition thought to be **state of starvation of organised fat of the cells of the tissues, upsetting normal metabolism.** This deficiency lessens the power of cohesion in the protoplasmic particles, which is the most powerful obstacle to the operation of chemical affinity. Growth, which results from chemical changes in the cells of the tissues, will be accelerated in proportion to the increased rate of chemical change, and a tumour results, appearing first in those cells which by previous irritation and more rapid repair have also been exhausted of their fats, bringing about molecular disturbance and causing the protoplasmic molecules to become arranged in a random manner. The cell envelope, also consisting largely of phosphatides becomes disorganised. Owing to this weakening, the protoplasm is allowed to sally forth, form irregular unions, and multiply illegitimately. Some of the nomadic cells are washed into the lymph stream and cause metastases; the defending cells being unable to resist them owing to a deficiency of organised fat. It is not to be held that all people who have at some time had glycosuria develop cancer. There must be a previous irritation of the site where the tumour develops. This theory may explain cancerous cachexia, which resembles the cachexias of other metabolic diseases. Death does not always result directly from the cancer, but from exhaustion of the cells of the organism, due to deficient supply of unsaturated fatty acid compounds. It may also explain the difficulty of transplanting animal cancers from one species to another, as each species has a characteristic fat. Occasional success with organic extracts, e.g. thyroid, thought to be due to the lipase-stimulating effect of these compounds.—J. T. Shirlaw, *Practitioner*, i/1929, 119.

For further notes on this theory and the sodium oleate treatment, see Vol. 2, pp. 753, 755.

Diet and Cancer. A report to the Ministry of Health by Monckton Copeman and Major Greenwood concerning an inquiry into the deaths from cancer in religious communities whose members live under strict dietary rules involving more or less complete abstinence from meat and rich and abundant food shows that the incidence of fatal cancer, either in females or males, in such communities is **not lower** than that in the general population.—*Brit. med. J.*, i/1927, 153.

The analysis of data supplied by monastic communities proves conclusively that fatal cancer occurs in populations abstaining from flesh food.—*Repts. publ. Hlth med. Subj.*, Lond., No. 36, 1916, *Lancet*, i/1927, 202.

In the discussion of a paper on the “**Causation of Cancer**,” by SIR WM. ARBUTHNOT LANE, SIR ARTHUR NEWSHOLME, while admitting that the theory of intestinal stasis as the cause of cancer was “feasible, ingenious and useful” queried why there was much more intestinal cancer in the male than in the female, and considered it difficult to explain by that theory why, in certain communities, chronic constipation associated with toxic absorption leads to a large increase in cancer of the breast, while in other countries there is more cancer of the uterus. Significant that in child-bearing women cancer of the uterus is more common than in single women and *vice versa* in the case of cancer of the breast.—*Int. Conf. Trop. Amer.*, 1924, 753, 759. The author in reply said that the cause was obviously traumatic.—*ibid.*

The Cancer Cell

The living cancer cell is the essential part of every cancerous growth, for when the cell dies it is impossible for any of the parts, agencies, or faculties of cancer to be excited or developed. In a successful graft the centrally placed cells die, but the peripheral portion of the transplanted tissue excites the surrounding fibrous tissue to form a support (stroma) for the tumour, whose so-called tissues are wholly developed directly from the implanted living cancer cell.

of the graft. A study of the cancer cell demonstrates that it is only a variation of a normal cell, for it possesses neither in structure nor in power anything not found in the healthy cell. Cancer cells possess a power of continuous multiplication, retaining inherited limitations to type of cells among which they first appear, but they develop and differentiate but little and irregularly in a manner neither purposeful nor effective.—*Brit. med. J.*, ii/1911, 766.

Cancer is a disease that generally arises in cells that are growing old, thus in woman the breast and uterus are prone to cancer as they get old before the rest of the body. The different incidence of cancer in the two sexes is the result of the special liability to the disease of organs possessed by one sex only. A chart showed the close parallelism of the cancer curve, in woman, and in their generative organs only (at 40 to 50 years of age), and the near approach of the curve for women, when we exclude disease of their generative organs, to that of men (at 50 to 60). Age, chronic irritation, X-rays, alcohol, are conditions that cause deterioration of the evolution of the individual cell.—Sir Alfred Pearce Gould, *Brit. med. J.*, ii/1910, 1836; *Lancet*, ii/1910, 1665; *Brit. med. J.*, ii/1912, 129.

Cancers are cells that have entered upon the degeneration of old age too soon and are being nourished by the juices and stimulated by the hormones of the younger and more vigorous tissues round them. Cancer cells are not young or progressive, but senile, regressive, and decadent. They are embryonoid, not embryonic, and for this reason they multiply incessantly and uselessly. Following the deductive process, the same forms of stimuli which act at one end of the developmental cycle to start a proliferation of progressive type ending in the formation of the normal human embryo, are capable of acting at the other end of the cycle to produce the embryoma-like proliferation of regressive type termed cancer, embryos being the tumours of the beginning of development, cancers being the embryomas of the end of development. With regard to predisposition, everything promoting degeneration in general is potentially a predisponent, e.g., the inadequate use of important organs, such as the reproductive organs of woman or the digestive organs of both sexes. Finally, cancer is a **cluster of cells** which, owing to over-stimulation and more diffuse degenerative influences, are **finishing their cycle of development too soon**, structure and function approaching the original simplicity and the primitive faculty of reproduction coming to the fore. Under the fertilising influence of the reproductive stimuli these cells burst forth into an embryonoid or amœboid reproductive activity and find their way along the lines of least resistance to all parts of the body.—H. Gilford, *Lancet*, i/1926, 858-862.

Describing cancer as due to cellular anarchy mistakes effect for cause; it is better to say that **cancer commences as cellular disorientation**. All organic functions being regulated by the nervous system, this system should be regarded as the origin of all derangements of function. A systemic reaction so profound as that produced by cancer cannot be due to a group of cells being in a state of anarchy. Traumatism in general, and chronic ulceration in particular, should be regarded as extending beyond the limits of organ or region, and as affecting simultaneously all the regional nerve supply.—J. Thomas, *Brit. med. J. Epit.*, i/1925, 82.

Warburg's Lactic Acid Theory. The cancer cell is distinguished above all by its power of rapid and uncontrolled growth. Such growth demands supplies of energy not liberated by hydrolytic reactions or lipase action. The main source yielding energy for growth in animal tissues is the tissue-respiration. Experiments have shown that there is no essential difference in respiration between normal and tumour tissues; the amount of oxygen consumed by the two does not differ markedly. Cancer cells differ from most normal cells, however, in their enormous production of lactic acid, which persists even when the cells are provided with all the oxygen of which they can make use—every hour a quantity of lactic acid equal to one-tenth of the dry weight of the tumour is produced. The breakdown of carbohydrate into lactic acid is a process in which considerable energy is set free. Thus, the tumour cell has at its disposal, besides its respiration, an additional source of energy not dependent for its existence on the oxygen supply of the tumour; for short periods the tumour cell can live under strictly anaerobic conditions, providing the tumour has an adequate supply of sugar. Nearly all tissues are able to form lactic acid when their respiration is damaged or suppressed. In tumours, therefore, the respiration has, to a large extent, lost the property, which it normally possesses in almost all normal tissues, of suppressing the lactic acid formation.—*Lancet*, i/1933, 30.

Prof. Bierich (Hamburg), speaking at the International Conference on Cancer (London, 1928), referred to the accumulation of lactic acid in cancer tissue. A cancer tissue was rich in the acid which invaded neighbouring tissues, breaking down barriers which might have hindered the progress of the disease.—*Brit. med. J.*, ii/1928, 105-109, 165-173.

With regard to the Warburg theory, experiments showed that high aerobic glycolysis of cancer cells cannot serve to distinguish cancerous from non-cancerous proliferations; a similar phenomenon had been observed in the study of cellular overgrowths produced by virus infections. As to the therapeutic possibility of affecting cancer growth by varying the oxygen pressure in the inspired air, this was found of no value, even within the limits of safety.—*Rep. Cancer Res. Fed.*, 1927-28, *Brit. med. J.*, ii/1928, 1018.

Cancer appears to be developed in precipitated **glycogen** in the liver or other organ. As the glycogen cannot be taken up by the normal cell tissue it is broken down and used by a dissipated sperm cell or species of yeast cell. It may be precipitated along with fibrin by a blow especially if situated near a vein. When a growth starts changes take place in composition of the bile salts, the patient becoming yellow or white in complexion. Cancer appears to be an asexual reproduction of the body.—Sir G. T. Beaton, *Lancet*, ii/1922, 655.

The Gene Mutation Theory offers a reasonable means of interpreting many of the ascertained facts about new growths. Good results are being obtained in experimental animals with the euglobulin fraction of anti-cancer serum from sheep, which causes first the local destruction of tumour cells and then causes an increased resistance resulting in a local cure.—*Brit. med. J.*, ii/1932, 117.

It is useless to look for the cause of malignant disease in the growth itself and the existing cause will eventually be found either in the blood or carried by the blood—probably some minute biochemical change affecting **reaction of the blood** on certain types of cell, cells that have suffered from a source of irritation or which are undergoing degenerative changes at the end of natural functional activity.—A. E. Barclay, *J. Amer. med. Ass.*, ii/1925, 1715.

On the Nature of Immunity to Implanted Malignant Tumours Immune animals inoculated with any transplanted tumour produce antibodies toxic to a wide range of malignant growths. The serum alone in the case of an animal immunised against a heterologous tumour, is lethal to *in vitro* culture of the antigenic tumour when sufficient complement is present, but the serum of an animal immunised against an homologous tumour only kills cultures of the antigenic tumour in the presence of leucocytes appropriately conditioned, or of some secretion from the latter. Thus, any malignant cell growing in a rat is in the absence of leucocytes, quite undamaged by antibodies present in this or any other rat's serum. Leucocytes only form their special cytase when extravasated, partial anaerobiosis probably being the determining factor.—T. Lumsden, *Lancet*, i/1927, 122.

In "**Protists and Disease.**" 1922, Jackson Clarke tells how in water-culture of *Molluscum contagiosum* the diagnostic corpuscles go through changes which prove them to be parasitic protists, and he names the species *Plassomyxa contagiosa*, and the group to which they belong Plassomyxineæ. Comparative study showed them to be nearly related to *Synchytrium*, a genus of fungi parasitic in the epidermal cells of plants. In certain stages they are in the plasmon state, i.e., the same state as true nucleoli or karyosomes. At other stages they are nucleated; or again, motile, as spironemes. In the Plassomyxineæ he includes the causal agents of smallpox, hydrophobia, syphilis and the common spontaneous human cancers and sarcomas. From X-ray and some other epitheliomas plassomyxines are absent, and for such growths the term "imitation-cancer" is used. This interpretation is opposed to that involved in the term "cancer cell" it is in harmony with results obtained by therapeutic doses of X-ray, radium, Coley's fluid, etc.—*Lancet*, ii/1921, 495.

Diagnosis of Cancer

Bendien's Test. The test is based on a flocculation reaction which occurs when a solution containing mixtures of sodium vanadate and acetic acid in slightly varying proportions is added to the serum. 20 different solutions of these sodium vanadate and acetic acid mixtures are placed in test-tubes containing

equal amounts of normal human serum. Flocculation begins in the tube containing mixture No. 6, rises to a maximum in mixtures 14 and 15 and then diminishes to the end of the series, disappearing in No. 20. If the serum has been inactivated previously by heating to 56° for half an hour the flocculation does not begin in No. 6 but only in 7. Bendien concludes that in certain pathological conditions a new type of protein appears in the serum, which he considers is confirmed by the fact that the flocculated material gives different and characteristic pictures on spectrophotometric examination. He states that flocculation below mixture 6 indicates the presence of cancer or tuberculosis and believes that a disposition to these diseases finds expression in a shift of the flocculation reaction which differs for the two diseases.—*Lancet*, i/1931, 1096.

The spectrophotometric test, employed for accuracy of diagnosis and as a confirmation of flocculation, is a highly technical process. The precipitate obtained with acetic vanadate mixture is heated to 56° to dissolve what Bendien calls "normal-labilin" (a protein present in all sera); it is filtered off, weighed, and suspended in NaHCO_3 (1 : 50). Suspensions, 20 in all, of various strengths, are submitted to spectrophotometric examination and 20 photographs of the ultra-violet part of the spectrum are taken. The absorption lines are plotted on a chart and a curve so obtained which is typical of cancer, indicating the presence of a thermostable protein peculiar to it.—A. A. Miller, *Lancet*, ii/1931, 427.

A criticism of the spectrophotometric aspects of the Bendien Test.—F. C. Smith, E. R. Holiday and J. Marrack, *Lancet*, ii/1931, 507; *ibid.*, 714.

The investigation Committee of the British Empire Cancer Campaign concludes that Bendien's method of diagnosis cannot at the present time be accepted as reliable.—C. Gordon-Watson, *Lancet*, ii/1931, 825.

A quantitative modification of the Bendien reaction described and the results of 600 tests detailed. Will differentiate malignant from non-malignant conditions in at least 95% of cases, clinical malignancy and degree of positiveness closely corresponding. The test is of no value in attempting to differentiate malignancy from pregnancy or to diagnose malignancy in a pregnant woman. A delicate and reliable test, more satisfactory as a laboratory technique than any other at present available and should be of value as a clinical aid to diagnosis and prognosis of malignancy especially in early cases.—E. Cronin Lowe, *Brit. med. J.*, i/1933, 407. See also *ibid.*, 484, 485, 536, 764.

The Cronin Lowe Serum Reaction, studied in an examination of 59 pathological cases, gave correct diagnosis in only 60% of cases. The method has no diagnostic value.—J. Paterson and J. Adler, *Brit. med. J.*, ii/1933, 1066. Unable to confirm Cronin Lowe's claims.—W. G. Listen and W. O. Kermack, *ibid.*, 1189; see also R. E. Jones and D. L. Woodhouse, *ibid.*, 1190; E. N. Allott, *ibid.*, 1190.

The control of prophylactic X-ray treatment of breast cancer by Cronin Lowe's modification of Bendien's Test. In addition to being found positive in all cases showing clinical activity (where X-ray treatment has improved the blood picture but not made it fully normal) it has also been positive in some post-operative cases showing no clinical evidence of disease, in some of which a satisfactory blood picture has been restored by X-rays, in others improvement only. The favourable response is due to some generalised action and is brought about by small repeated doses over a wide field. X-ray dosage for constitutional purposes requires individual control. If the vanadic acid test really gives an indication of metastatic activity in its microscopic stages there is a chance of doing something in time.—F. Hernaman-Johnson, *Brit. med. J.*, ii/1934, 534; see also E. Cronin Lowe, *ibid.*, 610.

Diagnosis of cancer by serum reactions.—J. A. Shaw-Mackenzie, *Lancet* ii/1922, 759.

Cancer and some of its significant chemical reactions. There is evidence of increase of **cholesterol** in the serum of carcinomatous patients and alteration in metabolism of fats and lipoids.—H. G. Reeves, *Lancet*, ii/1924, 726.

New flocculation reaction in malignant disease.—H. J. B. Fry, *Brit. med. J.* ii/1925, 4.

The determination of the serum bilirubin and the phenoltetrachlorophthalein test promise to be of assistance in the study of patients with abdominal carcinoma and suspected malignant disease of the liver.—per *Practitioner*, i/1926, 170.

The Botelho Reaction is based on the fact that with an acidified solution of iodine, cancerous serums give a permanent precipitate in the presence of definite quantities of the reagent; if physiological salt solution is added the results vary with the degree of dilution—a positive result obtaining with dilute serum, and a negative with concentrated serum; more definite results obtained by using serum with ascertained protein content (78% to 80%). TEDESCO-POLACK'S modification said to yield more definite and constant results, uniformity in the protein being secured by preliminary correction of the refractive index of the serum by means of the refractometer; the reaction is easy of manipulation and interpretation.—*Brit. med. J.*, i/1927, 109. See also *Lancet*, i/1926, 1157.

A series of papers on early diagnosis: skin, J. M. H. Macleod; tongue, D. C. L. Fitzwilliams; stomach, T. Izod Bennett; throat, L. Colledge; mediastinum, lung and pleura, L. S. T. Burrell; colon, W. H. Ogilvie; rectum, Sir C. Gordon-Watson; breast, G. Keynes; uterus, W. F. Shaw; bone, E. P. Brockman; bladder, A. E. Roche; prostate, H. P. Winsbury-White; testicle, C. Hope Carlton.—*Practitioner*, i/1933, 113-232.

Diagnosis of Carcinoma of the Stomach. SIR W. I. DE C. WHEELER stated that X-ray examination was the best method of diagnosis—analysis of gastric contents and fractional test-meal of little value. Venous thrombosis a valuable sign of early carcinoma of the stomach. If there were no gain in weight, after medical treatment, malignant disease should be suspected and exploration was more than justified. E. I. SPRIGGS agreed as to the importance of X-ray examination, and gave an account of the clinical manifestations. A. F. HURST considered the presence of blood in every part of a fractional test-meal evidence of malignant disease, unless there had been recent hæmorrhage from an ulcer. Character of "**resting juice**." The stomach should be completely evacuated before the meal. The "juice" often does not exceed 50 ml. in normals. More than 50 ml. and certainly more than 100 ml., suggests presence of some difficulty in gastric evacuation. Test for starch. If free hydrochloric acid is present, an ulcer is probable cause. If there is no free acid, and especially if the material removed is uniformly thick, a growth is almost certainly present, especially if foul odour and containing excess of organic acids. **Acidity:** In a consecutive series of 1000 fractional test-meals complete achlorhydria was found in 15.2%. The presence of free hydrochloric acid cannot be regarded as evidence against the diagnosis of a growth. **Blood:** Constant presence of, in association with achlorhydria, only observed in cancer of the stomach. A skilled radiographer could show an abnormality of the stomach in 100% of cases of malignant disease. Occult blood was present in 100% cases and should always be examined for; it was never present in normal people.—B.M.A. discussion, *Lancet*, ii/1925, 379; *Brit. med. J.*, ii/1925, 379.

EARLY RECOGNITION OF CANCER OF THE STOMACH.—(International Conference on Cancer, London, July 1928).—SIR BERKELEY MOYNIHAN stated that there were no symptoms pathognomonic of carcinoma in any of its stages; the symptoms were only suggestive, not conclusive. Examination by the radiologist, and by the chemist for blood in the fæces must be insisted on. A. F. HURST: Achlorhydria was not the result of carcinoma of the stomach but preceded its development. Many cases of achlorhydria were due to chronic gastritis which was found present in almost all cases of carcinoma of the stomach. A. J. WALTON: The hope for greater success lay not only in a wider recognition of the early symptoms but in a subsection of chronic ulcers in patients between 40 and 60 instead of prolonged medical treatment. D. P. D. WILKIE: The employment of a barium meal X-ray examination in all cases of obscure ill-health would reveal early cases of carcinoma when present, though clinical signs and symptoms were still

indefinite. T. IZOD BENNETT (London): A carefully performed gastric analysis yielded a reliable diagnosis in more than 90% of all cases.—*Brit. med. J.*, ii/1928, 105-109, 165-173.

Oleic Acid Method of Diagnosis of Gastric Carcinoma. The amount of Hübl's iodine solution, necessary beyond the normal limits, operating on gastric contents after a trial meal, indicates oleic acid.

One of the early signs of cancer of the stomach is a rapid falling off in the ferment activity and the percentage of inorganic chlorides is much increased.—Sir W. H. Willcox.—*Brit. med. J.*, ii/1928, 105.

Test Meals. The findings are not sufficiently definite to constitute facts on which a diagnosis can be made, except in respect of gastric carcinoma. The different stomach conditions are too variable to be pathognomonic in their value.—M. G. Henderson, *Practitioner*, ii/1929, 361.

For further details re Test Meals see section on Stomach Contents Examination, p. 357.

Occult Bleeding. Even a repeatedly negative test for occult bleeding does not rule out cancer of the stomach, especially when cancer of the pylorus is suspected.—E. Meulengracht and J. Jensen, *J. Amer. med. Ass.*, i/1929, 698.

For methods of detection see section on Examination of Fæces, p. 355.

Lactic acid has no specific relation to cancer of the stomach but it occurs in 50% to 70% of cases of gastric cancer and in only approximately 5% of cases suffering from all other diseases combined. A positive lactic acid test, while not pathognomonic of cancer, is unquestionably a helpful diagnostic sign and all patients in whom it can be demonstrated should be regarded as potential sufferers from gastric cancer till the diagnosis is disproved by radiological examination and an alternative explanation for the achlorhydria and stasis substituted.—L. S. P. Davidson and A. Calder, *Practitioner*, ii/1932, 605.

For methods of detection see section on Stomach Contents Examination. p. 360.

Treatment of Cancer

Anti-cancer Serum. By repeated injection of finely divided mouse carcinoma into a rat or rabbit a concentration of antibodies can be obtained in the serum which will kill cancer cells *in vitro*. Experiments on rats showed that the antiserum is definitely toxic and irritant, gives some cures in inoculated tumour and confers immunity. It is suggested that it might be possible to use an antiserum to prevent recurrence of tumour after incomplete surgical removal.—T. Lumsden, *Lancet*, i/1925, 383 and *Lancet*, ii/1925, 539.

Dr. T. Lumsden has demonstrated an antibody in the serum of rats with Jansen rat sarcoma in which a tumour has failed to grow or has regressed, after which a suspension of the tumour is repeatedly administered by intraperitoneal injection. The antibody is present in less amount in the serum of rats in which tumours are regressing, without artificial immunisation, but not in the serum of normal rats or of those bearing an actively growing tumour. The presence of this antibody is demonstrated by adding the serum to cultures of the growth, the consequence of which is that movement of the cells ceases and a series of changes follows which indicate unmistakably that these cells are dead. The chief difficulty in the interpretation of these findings is that the Jansen rat sarcoma is a tumour which frequently regresses—is it possible therefore to apply these findings to human cancer in which regression very rarely occurs?—Leader, *Brit. med. J.*, i/1935, 114.

Fichera's Biological Therapy. From experimental evidence that the tumour growth-inhibiting organisms *par excellence* are the spleen, the thymus, and the bone-marrow, extracts of these (and of lymph glands taken from freshly-killed calves) are prepared in saline in the presence of thymol and toluol in an incubator for 1 week to 2 months. Intravenous or intramuscular injections of 1 ml. are given twice weekly for several months. In 9% of 100 inoperable cases the tumour disappeared (in 3 cases a 3-years' cure, and in 7 a 2-years' cure), in 8% there was partial regression or condition remained stationary, and in further 20 cases improvement was claimed. 40 of the patients died, and in 20 the tumour was advancing.—*Klin. Wschr.*, Dec. 1933, 1957; per *Brit. med. J.*, i/1934, 66.

Four injections gave almost complete relief of pain in inoperable carcinoma of stomach, where morphine failed. Relief continued till death.—Max Honigsberger, *ibid.*, 132.

Treatment by connective tissue extracts is based on the theory that the excessive growth of cells is controlled by substance secreted in the connective tissue of their area. It is postulated that a factor exists to inhibit the tendency of living cells to reproduce themselves indefinitely and this inhibitory factor may be an enzyme, whose major function is lipolytic, and which is secreted in the connective tissues and functions to the best advantage in the area of its secretion. Treatment consists in introducing this essential substance into the carcinoma by intravenous administration of an extract of connective tissue derived from an area in the pig or cow corresponding to that of the primary growth of the patient. Encouraging results in 13 cases. The patient loses his cachectic appearance and the carcinoma diminishes in size and becomes attenuated in vigour.—H. Searl Baker, *Lancet*, ii/1933, 643.

Susman's Method. Based on the hypothesis that in cancer cases there is over-activity of the anterior pituitary, under-activity of the posterior pituitary and an increased demand for carbohydrate, cases of malignant growth in the human subject were treated with posterior pituitary extract (0.5 to 2 ml. daily) or with posterior pituitary extract and Theelin (0.25 to 0.5 ml. daily) the latter on the theory that an extract of the ovary would neutralise the hormone from the anterior pituitary. The patients were kept on a diet low in carbohydrate. Four cases treated with Pituitrin alone showed some temporary regression of the growth. Five cases treated with Pituitrin and Theelin showed some improvement.—W. Susman, *Brit. med. J.*, ii/1931, 794.

Treatment of carcinoma by injections of posterior pituitary extract and Theelin was considered, in some instances, to have a controlling effect on the growth of the tumour.—S. W. Houston and J. Miller, *Trans. Roy. Soc. Can.*, 1933, Section 5.

Nine cases treated after Susman's method at the Middlesex Hospital, with no benefit, except that in one case of epithelioma of the mouth there was diminution of the œdema of the tongue overlying the growth. In no case was life prolonged nor was there regression of any of the growths.—W. Riches and M. Kremers, *Brit. med. J.*, i/1932, 877.

Snake Venom. Analgesia lasting for 48 hours after injection in 26 cases of the venom of *Vipera ammodytes* subcutaneously in the arm or thigh of the diseased side every second day. The dose was 5 to 10 mouse units—one mouse unit, based on a mouse weighing 15 g., containing 0.00002 g. of the venom.—J. Korbler, *Klin. Woch.*, Aug. 18, 1934, per *Brit. med. J. Epit.*, ii/1934, 82.

Coley's Fluid is prepared by cultivating the streptococcus of erysipelas in bouillon ten days. *B. prodigiosus* is added, and the two are grown together for ten days. The culture is then killed at 60°. *B. prodigiosus* has a curative effect on tumours, and intensifies the virulence of the toxins of erysipelas.

The method was founded on the occurrence of retrogression in, and disappearance of, inoperable sarcomata as a sequel to attacks of erysipelas. Six weeks to three months treatment generally sufficient.

Coley's Fluid (of red colour) is supplied in phials of 2 ml. Dose: $\frac{1}{4}$ minim at first, injected into the tumour, or $\frac{1}{2}$ minim if injected elsewhere, diluted with sterile distilled water, gradually increased, e.g., by $\frac{1}{4}$ or $\frac{1}{2}$ minim daily, until a temperature of 102° to 104°F. is produced.

One ml. contains 600 million streptococci, 0.25% *B. prodigiosus* protein, and 13.3% glycerin.

Coley pointed out the necessity of following up this small dose by alternate local and *systemic* injections, also injections must be given until all reaction has calmed down and the temperature fallen.

Mixed-cell sarcoma treated locally; excision and Coley's Fluid $\frac{1}{4}$ to 3 minim doses, successful.—*Brit. med. J.*, ii/1913, 1484.

Chemotherapy. PROF. BLAIR BELL, speaking at the International Conference on Cancer, London, July 1928, said that in the synthetic preparation of a chemotherapeutic substance, e.g., a lead complex, not only should the specific agent in regard to growth and the malignant cell be considered, but also the special chemical constitution-function of the tissue in which the neoplasm has developed, and if it were possible to make a lead preparation absolutely specific for any one type of malignant growth it would appear that that preparation should vary according to the original tissue from which the neoplasm had sprung. It had been found that lead was detrimental to the cancer cell and the effects of radiation were augmented by the previous use of lead. There was considerable evidence to support the view that by itself lead, even in the crude preparations now used, could cause disappearance and apparent cure of malignant neoplasms and could sometimes beneficially effect leukæmia and other neoplastic conditions. PROF. W. J. DILLING said the successes obtained by lead treatment were greater than could be explained by spontaneous arrest or other causes. He expected a substance to be hit upon more effective than lead—but he did not expect a panacea. The aim was to find something which would retard the progress of the malignant cell without damage to surrounding tissues. BASIL HUME: Results with the lead treatment at St. Bart's. had been highly unfavourable. Cases so treated only lived for an average of 13 weeks, which was much less than their average expectation of life had they not been so treated. Grave health commenced in several as soon as treatment begun. STANLEY WYARD concluded that lead was of absolutely no value. A. P. THOMSON treated 55 cases, with favourable influence in 15, but improvement was only temporary. Colloidal lead better than lead glycine or colloidal lead phosphate. PROF. BLAIR BELL replied to the criticisms and said that it was at present admittedly a crude treatment. SIR THOS. HORDER in closing the discussion said that the differences in results with the lead treatment were possibly in part due to differences of technique, but no remedy was of practical value where the margin of safety between its lethal effect on the vital tissues and the resorptive effects upon the growth was less than that which admitted of reasonable control. He felt that the preparations of lead at present available had not yet arrived at the point of safety to enable them to advise their patients in this direction.—*Brit. med. J.*, ii/1928, 105-109, 165-173.

Exacerbation of the disease following the attempt to combine X- or radium-radiation with the earlier colloidal lead selenide treatment (D4S), led to the elimination of lead entirely—except for local application to ulcerated growths of lead amalgam ointment—and the substitution of two new colloids: a **sulphur-selenium colloid**, "*SSe*," and a **radio-active selenium colloid**, "*R.A.S.*," in which selenium is combined with feebly radioactive radium residues, radium-G and higher disintegration products. These two products are injected intravenously alternately, in combination with X-ray treatment. Of a series of 95 unselected cases, untreatable by surgeon and radiologist, approximately 20% have been restored to health and of the remainder a considerable fraction have shown temporary improvement.—A. T. Todd, *Brit. J. Surg.*, 1934, 619, *Brit. med. J.*, i/1934, 1080.

Lead in ionic form is too toxic for general application, but the lead complex employed at the Liverpool Medical Research Organisation have been found quite safe and gave no untoward results if controlled efficiently.—*Brit. med. J.* i/1935, 553.

NEW METHOD OF ADMINISTERING HEAVY METALS. The patient's blood was drawn off into sodium citrate solution, the corpuscles were centrifuged, washed, combined with the metal, washed twice or three times until the supernatant fluid was free of metal, and then reintroduced intravenously in a saline suspension. Animal experiments showed that it was possible to administer intravenously in this way doses of lead, copper, mercury, and other metals three to five times as great as would kill the animal if they were introduced intravenously in ordinary solution. The phenomenon is probably a surface effect of the nature of adsorption, or a specific combination of the metal with some constituent of the envelope of the corpuscle.—J. L. Jona, *Lancet* ii/1928, 15.

Injection of trypan blue, vital-new-red (Grübler), colloidal aluminium hydroxide, and sulphur were all found to cause diminished resistance to tumour growth in mice, and there was no evidence of any inhibitory action. As various colloids and semi-colloids are being tried for malignant disease in man from time to time, possible injudicious selection of the material, or inaccuracy in dosage may lead not to alleviation but to aggravation.—Ludford, *10th Sci. Re. Cancer Res. Fd, Brit. med. J.*, ii/1932, 766.

For details of the earlier work with lead and lead selenide in the treatment of cancer, see Vol. I.

Activated Fluorescein. Of 45 cases treated it was impossible to say that the use of fluorescein had influenced the action of the radiation in the slightest degree though some cases of ulcerated mammary carcinoma appeared to respond better. No differences were observable in response of mice fed with fluorescein and the controls but it appears that fluorescein has a mild antibacterial action which may sometimes turn the scale a trifle in the patient's favour.—H. J. Colwell, *Brit. med. J.*, i/1933, 457. See replies by S. M. Copeman and C. Goulesbrough, *ibid.*, 585.

For earlier work on activated fluorescein see Vol. I.

Butyric Acid—used in the form of a 50% mixture of kieselguhr powder and butyric acid—has a markedly selective and destructive action on cancer tissue, while it has a much less injurious effect on normal tissues. It is useful in cleaning up fungating malignant ulcers and rendering them suitable for treatment by surgery or radium. It can be made to destroy and delay the spread of growths in inoperable cancer of the rectum and stomach and it destroys superficial papillomata.—James Watson, *Lancet*, i/1933, 746.

Chloracetic Acids. The trichlor substitution-product was described by Prof. Heidenhain, for histology, in 1905, as a good tissue-fixing material. It penetrates even large masses of tissue and is useful for demonstrating the structure of epithelial organs. Roberts found it clinically of great value in rodent ulcer and benign epitheliomata and this biochemical research shows that it possesses both hydrophilic and oleophilic properties and dissolves lipoids. Experiments on carbohydrates and the parenchyme of fruits are detailed, and the reactions of normal and pathological skin in a variety of affections. The therapeutic effect in rodent ulcer and other epithelial growths is distinguished by solidification of the cell contents, with inhibition of leucocytes and watery transudation.—H. L. Roberts, *Brit. J. Derm.*, 1926, 323-334, 375-391.

Sodium Oleate.—Good results obtained by combined treatment with intravenous injections of 2 ml. of 2% sodium oleate (warmed previously to 30°), and oral administration of a *titanium lipase* compound, obtained by the action of a 10% solution of titanium tetrachloride on an aqueous solution of lipase prepared by the Willstaetter method.—D. Gardner, *J. trop. Med. (Hyg.)* 1928, 195.

Calcium Gluconate. Pain relieved by calcium gluconate intravenously (for rapid action) or intramuscularly (in 1 g. doses) and in addition large doses (2 g. thrice daily) by mouth, together with cod-liver oil to stimulate the activity of the calcium.—R. J. Behan, *Amer. J. Surg.*, Aug., 1932, per *Practitioner*, ii/1932, 419.

Urea. The offensive odour of a sloughing cancer in the terminal stage may be greatly reduced by packing the wound with urea crystals. Although

these dissolve in a few minutes the offensive smell becomes less with each application. Occasionally there may be pain in the wound after several days' treatment, but this can be relieved by morphine.—W. M. Millar, *J. Amer. med. Ass.*, i/1933, 1684.

X-ray and radium treatment is described under X-ray and radium therapy, see this volume, pp. 705 et. seq.

Cancer Statistics

Death rate. The death-rate per 100,000 in 1926 was 1362, as compared with 1336 in 1925, 1297 in 1924, and 1267 in 1923. These figures do not indicate an actual rise in incidence but that important factors in the apparent rise are more accurate diagnosis, improved certification of causes of death, and increased longevity resulting in a greater number of people reaching the age period of cancer than formerly.—Sir George Newman's Report for 1926, *Brit. med. J.*, ii/1927, 499. See also D. F. Shearer, *Lancet*, i/1928, 1225.

Half-a-million people die of cancer every year, of which Europe is responsible for 300,000 and N. America for 95,000. England's figure is 45,000, France 24,000, Italy 27,000, and Argentina 5,696.—per J. Amer. med. Ass., ii/1925, 1263.

Natural duration. From an analysis of 4,238 cases, Major Greenwood (*Rep. publ. Hlth med. Subj.*, Lond., No. 33, 1926) states that the mean duration in months for seven primary sites was found to be 38·3, 20·9, 26·7, 16·5, 12·0, 14·5, and 16·8 respectively in cancer of the breast, uterus, rectum, tongue and mouth, œsophagus, larynx, and stomach. There seems to be little relation between the age of onset and the duration. A **Survivorship Table** has been constructed calculating the chances of survival from 0 to 6 years after the onset of cancer in each region in untreated cases. The normal expectation of life of a woman of 55 is 18·87 years, that of a woman with untreated cancer of the breast is 3·25 years; that of one operated on under "average" conditions is 5·74 years, and of one operated on under the best conditions 12·93 years. Resort to early operation for cancer of the breast would add thousands of years to the active life of the nation.—*Lancet*, ii/1926, 188.

Statistics compiled from records of Middlesex Hospital over a period of 40 years. Two facts emerge: (1) the earlier the age of onset, the shorter the total duration of the untreated disease; (2) the natural duration of cancer at one and the same primary site is longer in the female than in the male.—W. S. Lazarus-Barlow, *Brit. med. J.*, ii/1924, 266.

From statistics based on 2000 cases (1900-1924) at the Cancer Hospital, S. Wyard concludes that no confirmation is given to the views of Lazarus-Barlow, and that the duration of life appears fairly even throughout all the age periods. Neither do the statistics indicate that the duration of life is greater in females than in males.—*Brit. med. J.*, i/1925, 206-7.

CANCER OF THE BREAST. The normal duration of unoperated cases (from onset to death) averages 3 years, and that of operated cases averages 5 years.—S. Wyard, *Lancet*, i/1925, 1181.

A 50% reduction in mortality from cancer of the breast and uterus could be achieved with present methods if all women would attend for radical operation at an early stage of the disease. At present the condition of little more than half the applicants is operable. Confirmed statistically on calculations based on survivals among known cases.—*Lancet*, i/1927, 303.

Incidence. The stomach is the seat of the disease in nearly 22% of the fatal cases in males in England and Wales. In females the generative and mammary organs are affected in more than two-fifths of the total cases.

In regard to the bowel, pancreas and prostate, cancer is relatively more common in people of high social status.—*Pharm. J.*, i/1926, 293.

Carcinoma of the œsophagus accounts for a proportion of all cases of malignant disease variously estimated at from 4% to 6%, the annual mortality from the disease in this country being about 1600, of whom 1200 are males and 400 females—it may be regarded as essentially a disease of elderly men, in which 80% of the cases occur at or below the bifurcation of the trachea.—H. S. Souttar, *Brit. med. J.*, ii/1934, 797.

Predisposing Causes. From a study of the cancer statistics of England and Wales, Holland and Italy, the Sub-committee is satisfied that *childbearing does not predispose the woman to cancer* of the breast and uterus. The higher incidence of cancer of the uterus upon married women is the consequence of

the immediate effects of a single parturition, and women who have borne many children are less, rather than more, liable to cancer of the uterus than married women who have borne few children.—The League of Nations Cancer Inquiry, *Brit. med. J.*, i/1926, 161.

There is no evidence to show that cancer is infective or contagious, nor has it been proved that hereditary disposition is of practical importance, or that any particular article of food increases or decreases an individual's liability, or that any danger exists in inhabiting houses in which cancer happens to have been exceptionally common.—*Min. of Health Report*, Aug. 14th, 1923.

"The transference of cancer from one individual to another must be rather rare, if taking place at all," and cancer certainly does not show a marked preference for certain families.—J. Thoner (from continued observations in Norway), *Lancet*, i/1925, 399.

The statistical association of cancer mortality and goitre.—P. Stocks, *Brit. med. J.*, i/1925, 84.

From experiments and observations, it appears that a *predisposition to cancer may be transmissible by heredity*.—P. Lockhart-Mummery, *Lancet*, i/1925, 427.

An interesting point raised in a Supplementary Report (No. 47) to *Rep. publ. Hlth med. Subj.*, Lond., No. 40, on Cancer of the Uterus, is the possible association of cancer of the uterus with miscarriage. It seems evident from the figures that the early termination of pregnancy before the foetus is viable has a definite association with the occurrence of cancer of the cervix.—*Brit. med. J.*, i/1928, 69; see also *Min. of Health Memorandum*, *ibid.*, 24.

Epidemiology. A report on the **geographical distribution** of cancer mortality—result of a questionnaire sent out in 1923 by the Office International d'Hygiène Publique. There is almost unanimous belief that mortality from cancer is on the increase, Norway alone not subscribing to this belief.—*Lancet*, i/1924, 352.

Incidence of cancer in Egypt—an analysis of 671 cases.—R. V. Dolbey and A. W. Mooro, *Lancet*, i/1924, 587.

Researches on the epidemiology of cancer in Iceland and Italy.—L. W. Sambon, *J. trop. Med. (Hyg.)*, 1925, 39-71.

Special cancer number. Observations and researches on the epidemiology of cancer in Holland and Italy (May-September, 1925).—L. W. Sambon, *J. trop. Med. (Hyg.)*, 1926, 233-287.

Cerebrospinal Fever

For a detailed account of characters, types of the Meningococcus Bacteriology and Diagnosis, Treatment and Disinfection of Carriers, and Antimeningococcic Serum, see Vol. I, p. 904 et seq.

The meningococcus is a very slightly pathogenic organism, but its feeble virulence is largely counterbalanced by its remarkable power of multiplying. The susceptibility, the lack of resistance of the organism, however—not its movement towards the meninges—constitutes the real reason why the general blood infection is, as a rule, of very short duration. As soon as the patient develops even the very slightest degree of immunity the meningococci present in the circulation are impaired in vitality, lose the power to bring about metabolic lesions, and finally are completely destroyed.—Ksawery Lewkowicz, *Lancet*, ii/1924, 488.

Meningococci may be found occasionally in peripheral blood films by using Giemsa's stain.—A. C. Coles, *Lancet*, i/1915, 750, 828, 1046.

Trypagar as a medium for culture of the meningococcus. Contains pea flour extract and trypsin broth as follows:—

(1) Pea Flour Extract

Mix pea flour 100 g., sodium chloride 100 g., with a litre of distilled water. Steam for $\frac{1}{2}$ hour with occasional stirring. Allow to settle and filter. Make fresh for each batch of trypagar.

(2) Trypsin Broth (Douglas)

To each $\frac{1}{2}$ kilo of fresh bullocks' hearts, freed from fat and vessels and minced fine, add 1 litre of water and make faintly alkaline to litmus with 20% potassium hydroxide solution. Heat slowly to 75° or 80° for 5 minutes. Cool to 37° and add 1% of Liq. Trypsin. Co. and keep at 37° for 2½ to 3 hours. Test for adequate peptonisation with Biuret reaction as below. Then render slightly acid with glacial acetic acid and bring slowly to boil for $\frac{1}{4}$ hour. Leave overnight in a cool place and decant the clear liquid. Make faintly alkaline to litmus and sterilise in autoclave at 118° for 1 hour on each of 2 days.

To Make Trypagar. Add 2% of agar and 0.0125% of calcium chloride to trypsinised broth made as above. Autoclave at 118° for $\frac{3}{4}$ hour to dissolve. Titrate a small quantity after well mixing with N/10 potassium hydroxide while boiling (phenolphthalein) and add KOH *q.s.* to the bulk to make *neutral*. Cool to 60°, add white of egg with shells (two to the litre) and autoclave again at 118° for 75 minutes or heat in the steamer for 2 hours. Filter and add 5% sterile pea flour extract and sterilise in the ordinary way.

The agar is directed to be cut up and washed with dilute acetic acid (2.5 ml. of glacial per litre of water) and again washed thoroughly before use.

Sterile blood serum is directed to be added to the trypagar in the proportion of 2% for use in primary cultures at the time of cultivation.

Biuret Reaction

To 5 ml. of broth add 0.1 ml. of 5% copper sulphate solution, mix and add 5 ml. of N/1 sodium hydroxide. A true pink shows an adequate, and a bluish-purple an incomplete, trypsinisation.—Lieut. Col. Gordon, Maj. T. G. M. Hine, Capt. M. Flack, *Brit. med. J.*, ii/1916, 678.

Chemical factors involved in growth of the meningococcus. The organism needs vitamins, as in Gordon's pea flour extract, for its primary growth *in vitro*, but during the early stages of subculture this need becomes greatly diminished. After a certain number of subcultures the organism will grow vigorously on a vitamin-free medium, providing there is an abundant supply of free amino-acid. The tryptic digest of casein (Cole and Onslow) fills these two conditions.—*Brit. med. J.*, i/1917, 11.

The meningococcus possesses both "rough" and "smooth" strains. Rough cultures are likely to be less potent antigens for the production of serum than smooth cultures.—G. F. Petrie.

Meningococcal Complement-Fixation Test. Technique used, that of the standard Wassermann reaction (No. 1 in *Spec. Rep. Ser. med. Res. Coun. Lond.*, No. 14), but instead of using a mixed suspension of local strains of meningococci all four types are included in known proportions. A saline suspension of pure cultures used containing in each ml. 90 million Type III, 60 million Type I, 50 million each of Types II and IV. Complement-fixation with meningococcal antigens appears in serum of at least 75% of cases of cerebrospinal fever, and a positive reaction in a case with meningeal symptoms is practically diagnostic of a meningococcal infection, though a negative reaction does not necessarily exclude this.—H. A. Cookson and J. E. Sinclair, *Lancet*, ii/1933, 634.

The polyvalent precipitin reaction with polyvalent antimeningococcal horse serum and the centrifuged spinal fluid is a reliable method of diagnosing meningococcal infections of the cerebrospinal system.—B. G. Macgrath, *Lancet*, i/1935, 545. Also *Lancet*, i/1934, 17.

Lange's Colloidal Gold reaction (see p. 352) has been criticised in regard to its validity as a test in diagnosis of neurosyphilis. It was found that a positive gold reaction in cerebrospinal fever is definite evidence of organic nervous disease.—C. Worster-Drought and co-workers, *Lancet*, ii/1922, 1063.

Epidemiology. Increased incidence in England shown by fact that number of deaths from 1929 to 1932 (588) exceeded total notified from 1915 to 1929. Highest rise in W. Riding of Yorkshire, where 885 out of the 2157 cases notified in 1931 occurred.—Sir G. Buchanan, *Bull. Off. int. Hyg. publ.*, 1932, 1098.

Yorkshire outbreak discussed by E. A. Underwood (*Publ. Hlth, Lond.*, 1933, 182). Disease most prevalent where ratio of children under 14 was highest. Children act as reservoirs for the meningococcus, and its virulence is raised by passage through them until it can produce meningitis in susceptible persons.

Colibacillary Infections. *B. coli communis* is a normal inhabitant of the intestines, but becomes virulent in certain conditions. It increases the virulence of typhoid. The *Bacillus coli* is present in an infant a few hours after birth.

The typical characters of *B. coli communis* are as follows:—

Gram-negative bacillus, producing acid and gas in glucose and lactose broths, acid and clot in milk, indole in peptone water, and fluorescence in neutral red. For further characteristics see *B. typhosus* and Bacteriological Examination of Water, this volume.

Alternative modes by which *B. coli* may bring about anaerobic decomposition of dextrose.—*Brit. chem. Abstr.*, 1928, A1159.

Types of *B. coli* associated with urinary infections investigated by Dudgeon, Bawtree and Wordley (*J. Hyg., Camb.*, 1921, 137). Hæmolytic types common in females. Hæmolytic strains have close antigenic relationships one with another.

Bacilluria and Pyuria. Bacilluria occurs with great frequency. 1. Associated with passage of pus; single abscess or more widespread infection of the urinary tract. 2. Milder stage—continuous passage of the bacilli but without pus or epithelial cells. 3. Intermittent passage of the bacilli. One often finds history of constipation, and a large proportion of cases are women.

In examining such urine in which pus is absent note: (a) Pale colour, paler than one would expect from the gravity. (b) Low acid reaction; rarely very acid. (c) The urine is hazy, not clear. Filter a little, if still cloudy, examine under the microscope ($\frac{1}{2}$ in. oil immersion). Round bodies or short rods (the former are the bacilli "on end"). Note motility. Stain centrifuged deposit by Gram's method. The organism is gram-negative. The urine should be fresh and collected in a sterile flask, by catheter if possible. Inoculate an agar tube with a large loopful—note opaque white growth with crenated margin after 24 hours also on rebipelagar or Conradi Drigalski medium.

Estimate the Acid Index by titrating 10 ml. of the urine with N/10 sodium hydroxide, using phenolphthalein. If low, administer sodium acid phosphate thrice daily in order to increase the acidity up to even 10° and to keep it up. Albumin (due to globulin probably due to leucocytes) may be found, also acetone.

The chief bacteria concerned are *B. coli*, streptococci of the long type, which are more feebly gram-positive than *S. pyogenes*, staphylococcal forms and "beaded" bacilli of the *B. xerosis* type, also a great variety resembling *B. proteus vulgaris*. All of these have been found in bacilluria with joint troubles, but the most striking cases afford almost pure cultures of streptococcal form closely resembling the *Streptococcus salivarius*, a common inhabitant of the throat. Tubercle bacilli should always be looked for, especially if lymphocytes are present. Pneumococci are said to occur, but only in connection with acute cases whilst gonococci play an important rôle by themselves.

B. COLI IN THE BLOOD. Blood cultures made from persons suffering from undoubted coli infections are almost invariably sterile. On three occasions pure growths of the bacillus were obtained from the blood. In two cases they were obtained whilst patients were actually suffering from a rigor and in the third $3\frac{1}{2}$ hours after a rigor.—*Lancet*, ii/1912, 1500.

Infection of the blood stream by *B. coli* relatively uncommon. The chief portals of entry in order of frequency are the urinary tract, the female genital tract, and the intestinal tract. *B. coli* sepsis occurs more frequently in women of from 20 to 40 and in men from 40 to 70.—*J. trop. Med. (Hyg.)*, i/1924, 19.

Treatment of urinary infections with ketogenic diet; i.e., minimum of carbohydrates, small quantity of protein and maximum quantity of fat to render urine acid; at pH 5.5 urine is strongly bactericidal.

Example of a Week's Ketogenic Diet

	Breakfast	Lunch	Tea	Supper
Monday	1 oz. pressed beef, roll, $\frac{1}{2}$ oz. butter, tea (with 1 oz. cream).	Tomato soup (4 oz. cream, 1 tomato, stock), 2 oz. cutlet, 3 oz. spinach, roll, $\frac{1}{2}$ oz. butter. Coffee cream mould, with 1 oz. added cream, lemonade.	Salad (2 oz. with lettuce, cress, cucumber, or a little celery), 2 rolls, $\frac{3}{4}$ oz. St. Ivel cheese, 1 oz. butter, tea (1 oz. cream).	$1\frac{1}{2}$ scrambled eggs (using 1 oz. butter), roll, $\frac{1}{2}$ oz. butter, rhubarb fool (4 oz. fruit, 4 oz. cream), coffee (1 oz. cream).
Tuesday	1 oz. ham, 1 oz. salad, $\frac{1}{2}$ oz. butter, tea (with 1 oz. cream).	Soup (4 oz. cream), 1 oz. beef, $\frac{1}{2}$ oz. fat, 3 oz. cabbage, roll, $\frac{1}{2}$ oz. butter. Choc. cream mould, with 1 oz. extra cream, lemonade.	Boiled egg, 1 roll, $\frac{1}{2}$ oz. butter, tea (1 oz. cream).	$\frac{3}{4}$ oz. St. Ivel cheese and salad, 2 rolls, 1 oz. butter, gooseberry fool (4 oz. fruit and 4 oz. cream), coffee (1 oz. cream).
Wednesday	1 oz. bacon, 1 egg, roll, $\frac{1}{2}$ oz. butter, tea (with 1 oz. cream).	Cream tomato soup, 2 oz., steamed fish, $\frac{1}{2}$ oz. butter. Coffee cream mould, with 1 oz. cream, lemonade.	$1\frac{1}{2}$ scrambled eggs (1 oz. butter), roll, $\frac{1}{2}$ oz. butter, tea, (1 oz. cream).	$\frac{3}{4}$ oz. St. Ivel cheese and salad, 2 rolls, 1 oz. butter, rhubarb fool (4 oz. fruit, 4 oz. cream), coffee (1 oz. cream).
Thursday	$1\frac{1}{2}$ scrambled eggs (with 1 oz. butter), roll, $\frac{1}{2}$ oz. butter, tea (1 oz. cream).	Cream soup, $1\frac{1}{2}$ oz. steak, 3 oz. spinach, roll, $\frac{1}{2}$ oz. butter. Choc. cream mould, with 1 oz. cream, lemonade.	$1\frac{1}{2}$ oz. tinned salmon, 2 rolls, 1 oz. butter, tea (1 oz. cream).	Egg salad (1 egg with lettuce, cucumber, cress), roll, $\frac{1}{2}$ oz. butter, gooseberry fool, coffee (1 oz. cream).
Friday	1 oz. ham, $\frac{1}{2}$ portion of salad, 1 roll, $\frac{1}{2}$ oz. butter, tea (1 oz. cream).	Cream tomato soup, 2 oz. steamed fish, $\frac{1}{2}$ oz. butter, 1 roll, $\frac{1}{2}$ oz. butter. Coffee cream mould, with 1 oz. extra cream, lemonade.	$\frac{3}{4}$ oz. St. Ivel cheese and salad, 2 rolls, 1 oz. butter, tea (with 1 oz. cream).	Cheese omelette (1 egg), roll, $\frac{1}{2}$ oz. butter, rhubarb fool, coffee (1 oz. cream).
Saturday	1 oz. bacon, 1 egg, roll, $\frac{1}{2}$ oz. butter, tea (1 oz. cream).	Cream soup, 2 oz. chicken, salad. Choc. cream mould, with 1 oz. cream, lemonade.	$1\frac{1}{2}$ scrambled eggs (1 oz. butter), roll, $\frac{1}{2}$ oz. butter, tea (with 1 oz. cream).	$1\frac{1}{2}$ oz. tinned salmon, 2 rolls, 1 oz. butter, gooseberry fool, coffee (1 oz. cream).
Sunday	$1\frac{1}{2}$ scrambled eggs (1 oz. butter), roll, $\frac{1}{2}$ oz. butter; tea (1 oz. cream).	Cream tomato soup, 1 oz. roast beef, $\frac{1}{2}$ oz. fat, 1 roll. Coff. cream mould, with 1 oz. cream, lemonade.	$\frac{3}{4}$ oz. St. Ivel cheese, 2 rolls, 1 oz. butter, tea, (with 1 oz. cream).	$1\frac{1}{2}$ oz. cold chicken, salad, roll, $\frac{1}{2}$ oz. butter, gooseberry fool, coffee (1 oz. cream).

Supplementary Notes on Diet

Only saccharin may be used for sweetening.

Total fluid intake restricted to 2 pints in the 24 hours. Lemonade made with fresh lemons and saccharin. Plain soda-water allowed.

Synthetic cream. Salt-free butter essential for making. Casein solution made up daily by dissolving 1 oz. soluble light white casein in $1\frac{1}{2}$ pints water, steaming in a double cooker and straining through muslin before use. To make the cream 3 oz. of this solution, warmed with a little saccharin, is mixed with 2 oz. of melted butter and pumped through a cream machine. Ice-cream can be made by mixing this cream with gelatin and eggs and some flavouring in an ice and salt box.

Soups are prepared from bone and meat stock with cream, but without potato or thickening. Tomato, Lemco, Marmite, or bay leaves can be used for flavouring. A helping contains 4 oz. cream.

Vegetables. Brussel sprouts, cauliflower, or kale may replace cabbage and spinach, but not more than 3 oz. allowed at any one meal. White sauce made with flour not allowed.

Salads. Small amounts of olives or asparagus may be taken with salad but total helping should not exceed 2 oz. If salad dressing is used, it should be home-made—with olive oil, eggs, and vinegar. If tinned or bottled fruit is used it should be first tested to make sure it is practically sugar-free.

The rolls used are Callard's gluten dinner rolls—4 or 5 per diem with plenty of butter.

Puddings. The "chocolate cream mould" contains 2 oz. of casein solution, 2 oz. of cream, $\frac{1}{12}$ oz. of gelatin, $\frac{1}{4}$ oz. of grated Callard chocolate, 1 gr. of saccharin, and is made as follows: Put casein solution, cream, saccharin, and half the chocolate into a saucepan with gelatin. Gently heat to dissolve, and pour into mould. When set, turn out and decorate with remaining chocolate and whipped cream, or put all chocolate into mould and serve with cream. 1 oz. extra cream should be used.

The "coffee cream mould" contains 2 oz. of casein solution, 2 oz. of cream, $1\frac{1}{2}$ oz. of strong coffee, $\frac{1}{12}$ oz. of gelatin, 1 gr. of saccharin, and is made as follows: Melt gelatin in coffee with saccharin; when melted, strain, add the casein and mix the cream. Pour into mould and serve with 1 oz. of cream.

Other similar puddings may be prepared from eggs, gelatin, and cream with lemon or vanilla flavouring.

Night Feeds. In order to avoid too long a period without fat absorption it is advisable to give a cup of cocoa with an ounce of cream or some other fatty food in the middle of the night.

Drugs—in particular, alkalis or potassium citrate—should be avoided.—A. T. Fuller and L. Colebrook, *Lancet*, ii/1933, 736.

Diet sheets and technique of method used at Mayo Clinic.—A. L. Clarke *Lancet*, ii/1932, 511.

A warning as regards unlimited lemon drinks. Used extensively they increase the alkaline excretion in the urine to such an extent as to make even a urine with a heavy ketone excretion definitely alkaline.—R. D. Lawrence *Lancet*, ii/1933, 839.

Normal diet has 300 g. carbohydrate; it must be reduced to 15 or 30 g. before adequate ketosis is produced.—D. M. Dunlop, *Proc. R. Soc. Med.*, 1933, 217.

Treatment of coli bacilluria by ketogenic diet; method of making diet inoffensive to patients who have to reconcile themselves to 240 g. of fat daily.—C. M. Wilson, *Lancet*, ii/1932, 960.

Principal factor inhibiting growth of bacteria in urine under ketogenic diet is *l*- β -oxybutyric acid.—A. T. Fuller, *Lancet*, i/1933, 855.

Treatment of pyuria in children by ketogenic diet first recorded by H. F. Helmholtz (*Proc. Mayo Clin.*, 1931, 609).—*Acta pædiatr.*, Stockh., 1932, 195. *J. Amer. med. Ass.*, ii/1932, 1305.

If no abnormality is present, ketogenic diet is probably an efficient method of clearing up any urinary infection, but doubtful if it has any advantage over older methods of treatment.—J. B. Rennie, *Arch. Dis. Childh.*, 1933, 47.

Treatment of urinary infections in the puerperium by a ketogenic diet. In 24 out of 54 cases the urine became sterile within 17 days—in 10 cases within a week. The number of cases in which sterility was obtained was directly

proportional to the degree of ketonuria.—A. T. Fuller and L. Colebrook, *Lancet*, ii/1933, 735.

Of 16 cases of urinary tract infection, 5 were cured completely by treatment with ketogenic diet: 4 were cured following addition of ammonium nitrate to the treatment: and 2 following addition of hexamine: 5 were improved but the urines were not sterile. No symptoms were caused by the hyperacid urine, and only 1 case had gastric upset. Unsuitable for out-patient departments.—D. C. Robb, *Brit. med. J.*, ii/1933, 1162.

Treatment with Mandelic Acid. Mandelic acid given as the sodium salt in 3 g. doses four times daily in conjunction with ammonium chloride, found effective in cases of urinary infection unassociated with obstruction.—M. L. Rosenheim, *Lancet*, i/1935, 1032.

Abnormal Putrefaction in the Intestine. The presence of anaerobic bacteria is believed to account for this—normally the bacteria are either aerobic or facultative anaerobes mainly, whilst the anaerobic are in the minority. Excess of the anaerobic bacteria may be caused by excess of animal food,—auto-intoxication can undoubtedly be traced to this. Again the food may be excessively contaminated with bacteria, e.g., in pyorrhœa alveolaris and post-nasal catarrh. Further, it may pass from the stomach imperfectly digested. There is in addition purely intestinal putrefaction. One of the agencies of defence by nature against such injury is the combating of toxins by the intestinal flora—principally *B. coli*—this organism is furthermore stated to produce thermolabile and thermostable substances which not only inhibit the growth of other organisms but also their own if given enough time to act.

Diagnosis of abnormal putrefaction may be assisted by examining (1) URINE: increase in ethereal sulphates in the urine; increase in total output of aromatic bodies; rise in capillary constant; examination for indican and other constituents. (2) FÆCES: staining by Gram's method and counterstaining with neutral red—the *red organisms should preponderate*. In abnormal putrefaction, in proportion as the aerobic bacilli are replaced by strict anaerobes (mostly gram-positive) the blue stained will be in excess. A loopful of a 1 in 100 suspension of fæces in sterile milk should not produce a rapid gas formation (e.g., by *B. ærogenes capsulatus*).

Variability in the gas-forming power of intestinal bacteria. It is possible to select a strain of *B. coli* which fails to produce gas from certain mono, di-, and poly-saccharides.

A new Index of Intestinal Putrefaction based on the liberation of tyrosin. To 50 ml. of urine add 5 ml. of 25% sulphuric acid and extract by shaking with 15 ml. of ether. Pour off 2 ml. of the ether into a dry tube and evaporate by dipping into hot water. Take up residue in 2 ml. of water. Add Millon's reagent drop by drop, and boil. Red coloration indicates positive reaction. Cheese taken during preceding 24 hours interferes with the reaction: aspirin and salicylates should also be excluded. A positive reaction rarely obtained in the absence of indican or urochrome. Excretion definitely encouraged by ileal stasis, *B. coli* infection of the ileum, and hypochlorhydria. Positive reaction definite evidence of serious absorption of bacterial products from colon or small intestine.—N. Mutch, *Lancet*, i/1929, 1034.

Dengue. Dengue, which is thought to be due to a filtrable virus, resembles sand-fly fever but the febrile period is longer and relapse is more common. Sand-fly fever occurs in all the countries round the Mediterranean and extends into India; dengue occurs typically in Australia, but is recorded from India, Africa, and other places. Rheumatic-like pains in the febrile stages constitute the chief symptom.

An undesirable degree of complication has been imparted to the subject. Claims to the discovery of "new" diseases would in most cases be recognised as unjustified if the authors were aware of the following facts in connection with the fevers of the dengue group. (1) Fevers of the dengue sand-fly group may last from 1 to 7 days. (2) They show a great variety of symptoms—in

fact, the only common clinical features are the sudden onset and short duration. (3) They are extremely common and widespread over the tropical and sub-tropical world. (4) They may occur as sporadic cases in an endemic area, or as intense epidemics.

If dengue is regarded as a disease in which break-bone pains, a two-phase fever and a secondary rash are essential features, it is not surprising that medical men should look upon outbreaks of fever in which these characteristics are absent as distinct diseases.—J. W. D. Megaw, per *J. trop. Med. (Hyg.)*, 1923, 347.

The insect vector of dengue, in Manila and probably elsewhere, is *Aedes ægypti* (*S. fasciata*, as it used to be called), confirming the work of Cleland Bradley and McDonald in Australia; it is not *Culex quinquefasciatus* (formerly known as *C. fatigans*).—*Brit. med. J.*, ii/1926, 489.

Transmission and aetiology.—*Indian med. Gaz.*, 1925, 377; see also A. C. Chandler, *ibid.*, 460.

Observations in Greece showed that the disease could be transmitted by direct inoculation of filtered or unfiltered blood, and by direct transmission through *Aedes argenteus* (*Aedes ægypti*). The mosquito became infective 11 days after feeding and remained so as long as it lived.—*Lancet*, ii/1928, 1348.

Points of similarity between yellow fever and dengue.—*Brit. med. J.*, ii/1917, 105.

The differential diagnosis of dengue and influenza.—E. P. Thurston, per *J. trop. med. (Hyg.)*, 1933, 344.

Recent epidemics of dengue.—*Brit. med. J.*, ii/1928, 806.

Diphtheria. As seen in young cultures, *Corynebacterium diphtheriæ* occurs in the form of straight, or more frequently slightly curved, rods which measure usually about 3μ to 4μ in length and about 0.5μ in thickness, being rounded or tapered at their ends and staining unequally, the staining occasionally giving a sort of barred marking. They contain granules which produce a beaded appearance and which with certain dyes give a metachromatic action, e.g., staining a purplish tint with polychrome methylene blue. They are stained a deep, almost black colour with Neisser's and other similar stains. The ends of the bacilli may become swollen, especially in the longer forms; later these may form club-like structures which stain deeply, whilst the protoplasm becomes broken up into globules. Other bacilli may become thicker and segmented, and various stages of disintegration are seen. A characteristic feature in a film is the arrangement of the bacilli, which lie at various angles to one another giving an appearance similar to Chinese letters or cuneiform characters. Size and general appearance vary with different strains of organisms, with different media, and with the duration of the growth. Sometimes quite sharp types are met with, and rarely, in tryptic digest broth, the culture may consist wholly of coccoid forms, arranged in clumps, diplococcal forms, and chains.—Muir and Ritchie.

Anderson, Happold, McLeod and Thomson (*J. Path. Bact.* 1931, 667), describe two forms of diphtheria bacilli, **gravis** and **mitis**, the former associated with the severest cases with a high death rate, and the latter with milder attacks and a lower death

rate. The main bacteriological characteristics of *gravis*, *mitis*, and *intermediate* forms were as follows:—

Gravis ferments starch and glycogen: pellicle and granular deposit in broth: grey or grey-black colony on chocolate-tellurite medium.

Mitis does not ferment starch or glycogen: uniform turbidity in broth: black colony (often partial inhibition of growth) on chocolate-tellurite.

Intermediate does not ferment starch or glycogen: granular growth in broth.

Parish, Whatley and O'Brien do not agree that *gravis* strains are solely, or even mainly associated with severe forms, as they found *mitis* strains at least as virulent, and under laboratory conditions *mitis* strains have produced much better toxins than *gravis*. They suggest instead of *gravis* a non-committal title such as "starch-fermenting type."—*Brit. med. J.*, ii/1932, 915; see also *ibid.*, i/1934, 299.

Starch fermentation by the *gravis* type of diphtheria.—J. S. Anderson and co-workers, *Lancet*, i/1933, 293.

Direction for collecting specimens. If a sterile swab is not at hand, a small piece of absorbent cotton wool should be steamed, allowed to cool and rubbed over the membrane on the fauces of the patient and removed in a test-tube or bottle which has been similarly sterilised. If possible, a small portion of the membrane should be detached in addition. The organism may persist for many months in nasal and aural discharges also in dry condition, an important point to recollect in disinfection of bed linen. Moist heat destroys the organism rapidly, e.g., a temperature of 60°. Is also very sensitive to treatment by antiseptics. Nurses in charge of patients should be examined occasionally, as the organism may be present without symptoms of illness, and infection by such agency should be guarded against. An injection of antitoxin or other form of diphtheria prophylactic is a safeguard.

Films are prepared from the swab. Stain by Gram's method (gram-positive) also by Pugh's or Neisser's stains to show metachromatic granules. Dry and mount in xylol balsam.

Neisser's method of staining the organism:—

Stain $\frac{1}{2}$ minute each (washing between with water) with

- A. Methylene blue, 0.5 g.
Dehydrated alcohol, 10 ml.
Distilled water, 475 ml.
Glacial acetic acid, 25 ml.
- B. Bismarck brown, *syn.* Vesuvine, 1 g.
Distilled water, 500 ml.

The length of time each stain is used has been much altered by various workers. Originally it was a matter of 3 seconds with A and 10 seconds with B. The method can be used for examining direct from the swab.

The use of eosin solution instead of B above gives good results, working as follows:—

1. Make film in usual manner. 2. Stain with A 3 minutes, and without washing pour on Gram's iodine solution 1 minute. 3. Wash in water and counterstain with eosin 5% aqueous solution 3 minutes, wash, dry and mount. This method was claimed to be diagnostic, but other organisms, e.g., *B. xerosis*, *B. proteus zenkeri*, *B. cyanogenus*, and various organisms found in water, give similar results. The granules are stained blue, the rest of the bacillus is stained by the counterstain.

Good results direct from the swab are obtained by the following:—Stain with alkaline methylene blue 3 to 4 seconds, afterwards with B above.

Pugh's (syn. Ponder's) Toluidine Blue Stain.—Toluidine blue 0.02 g., glacial acetic acid 1 ml., dehydrated alcohol 2 ml., water to 100 ml. A loopful

of the stain is dabbed on the dried smear and examined as hanging drop with 1/12th in. oil immersion lens. Used for direct examination from the swab, the appearance is characteristic. *C. diphtheriæ* appears pale blue with bright and often deeply stained red granules along its entire length, some yeasts and sarcinae also show the metachromatic markings. Hofmann's bacillus stains dark blue with a light band. Diphtheroid bacilli cannot be mistaken or confused with *C. diphtheriæ* by the method. It would be well to make the film, if possible direct from the throat. A negative result is not to be considered of much value. Vincent's angina fusiform bacilli also stain dark blue. The method is claimed to be simple and rapid.—Constant Ponder, *Lancet*, ii/1922, 23. (*Stitt finds it better than Neisser's*).

It can be stated with confidence that in the majority of cases of acute diphtheria from which a satisfactory swab has been taken the disease can be diagnosed on examination of the direct smear. Of 76,000 "acute" swabs so examined during 23 years the diphtheria bacillus has been detected in 85%. It should be remembered, however, that in adults diphtheroid organisms are sometimes seen which resemble the diphtheria bacillus from a child's throat, and it is not advisable to report on direct smears taken from patients over the age of 18. By this method the regrettable "waiting for the result of cultivation" would in many cases be avoided.—C. Ponder, *Brit. med. J.*, ii/1934, 373.

Roux's Stain for Bacteria.—Dahlia or gentian violet 0.5 g., methyl green 1.5 g., distilled water 200 g.

Sections of Membrane.—Stain for the diphtheria bacillus by the Eosin-Gram method:—

1. Stain 4 or 5 minutes with eosin solution. 2. Wash well in water. 3. Pass through a little alcohol. 4. Stain with aniline-gentian-violet, 10 minutes. 5. Cover with Gram's iodine solution, 3 minutes. 6. Decolorise with aniline oil. 7. Clear with xylol and mount in xylol balsam.

Pseudo-varieties. Two reputed pseudo-varieties; one morphologically and in all respects similar to the specific organism, but non-virulent, the other **Hofmann's Bacillus**. This stains more regularly than the diphtheria bacillus and shows no polar staining. Uniform in shape, size and staining.

The general trend of opinion is that the *Hofmann bacillus* is quite distinct but Hewlett thinks that it really includes several species of which one may be a modified form of the diphtheria bacillus.—*Brit. med. J.*, i/1912, 75.

It is said that 10% of people normally harbour such as against 1% to 2% with granule types.

Reports on swabs from throat and nasal passages. Presence of Hofmann's bacillus of no clinical significance.—J. L. McCartney, *Lancet*, ii/1928, 514, 565.

B. xerosis occurring in xerosis conjunctivæ, also in nose, throat and ear differs in the fact that primary cultures from the eye on blood serum first appear in 36 hours. Sub-cultures do not show this difference. The organism is non-pathogenic to guinea-pigs.

Characters: gram-positive and very similar to *C. diphtheriæ*: often occurs in the throat.

Koch-Weeks bacillus, a thin, non-motile organism decolorised by Gram's method, is found in a large number of cases of conjunctivitis. A diplobacillus has also been found which causes an extremely dangerous form of conjunctivitis, but is amenable to treatment.

B. Morax-Axenfeld. Angular conjunctivitis is the only form of conjunctivitis in which the clinical appearance is characteristic of the organism at work—the diplobacillus of Morax-Axenfeld (gram-negative).

Pathogenicity of true diphtheria bacillus compared with pseudo-forms. 5 ml. of a glucose-broth culture 2 days old with pseudo-diphtheria bacilli are non-pathogenic to guinea-pigs, whereas $\frac{1}{2}$ ml. of a similar culture of true diphtheria bacilli usually kills in 2 days.

Cultivation

Cultivate on Loeffler's blood-serum—fine cream-coloured growth in 1 to 16 hours, and stain the film from this with methylene blue, Neisser's or Gram's method. Cultivations should in all cases be made on blood serum or glycerine agar before the result of diagnosis can be positive. Further characteristics—no spores, non-motile. Form differs with culture medium.

Gordon and Hine's Legumin Trypagar (*q.v.*), with the addition of 0.3 ml. of sterile 1% telluric acid to 10 ml. of the agar, is a good medium for growing *C. diphtheriæ*. The majority of organisms other than diphtheroids reduce the

telluric acid and produce blackish colonies. Especially is this the case with the staphylococci; the streptococci do not reduce the telluric acid. The diphtheroid colonies are greyish-white, about 1 mm. in diam., semi-translucent, slightly convex and have a slightly darkened central spot.—D. R. Wood, *Brit. med. J.*, i/1921, 562.

Glucose Litmus Broth cultures of true diphtheria bacilli show marked acidity in 24 hours, while those of the pseudo-forms are stated not to evince this alteration of reaction. *This method is useful for confirmation where no licence for inoculation of animals is held.*

Serum-water gives good result:—

Coagulate blood serum in an equal quantity of water, filter, add to one half 1% dextrose, and to the other 1% sucrose. Add neutral red as indicator. After 24 hours a marked acidity is produced in the glucose tube by *C. diphtheriæ*, in both the glucose and the saccharose tubes by *B. xerosis*, and no change is produced in either tube by Hofmann's bacillus.

Diphtheria Antitoxin

Preparation. Diphtheria antitoxin consists of the fluid separated from coagulated blood of the horse immunised by inoculation with diphtheric toxin, produced by the filtered culture of the *C. diphtheriæ* in broth—a surface growth is important. Repeated injections during 4 to 6 months of increasing quantities of toxin, up to as much as $\frac{1}{2}$ or 1 litre, render the serum of high antitoxic quality. When the horse's serum has acquired a sufficiently great antitoxic property, the horse is bled about 10 days after the last injection and the serum prepared for use as a remedy, and as a prophylactic.

Standard. The international standard for diphtheria antitoxin was adopted in *B.P.* '32 as the basis of a British standard. The international standard is a quantity of dried antitoxin kept in the Serum Institute at Copenhagen, while the British standard is a quantity of similar material kept at the National Institute for Medical Research.

The Unit. The unit is the amount of activity in a fixed amount of the international standard. The British standard has been carefully compared with the international standard so that the weight of the British standard containing 1 unit is accurately known.

Methods of Assay. The method suggested in *B.P.* '32 directs those wishing to assay unknown samples of antitoxin to prepare first of all a suitable sample of diphtheria toxin. This is obtained by growing the *C. diphtheriæ* on the surface of broth and then killing the organisms by the addition of phenol. Mixtures are then made containing different amounts of this toxin together with 1 unit of antitoxin, and these mixtures are injected into guinea-pigs to see whether they die. The smallest amount of toxin which, when mixed with 1 unit of antitoxin, will cause the death of a guinea-pig in 4 days is said to be the L_{\dagger} dose of toxin. Unknown samples of antitoxin are then tested by preparing mixtures containing different amounts of antitoxin with the L_{\dagger} dose of toxin, and these mixtures are injected into guinea-pigs. The mixture which causes death in 4 days contains 1 unit of antitoxin.

This method, which has been long established, has been largely replaced in practice by a skin reaction test. The smallest dose of toxin is found which, mixed with 1 unit of antitoxin, causes redness when injected into the skin of a guinea-pig. This dose of toxin is called the L_r dose. Mixtures of the L_r dose with different amounts of unknown antitoxin are then injected to find which mixture just causes a reaction. The amount of antitoxin in this mixture is one unit.

A good **culture medium** is bouillon with 1.5% Witte's peptone, 0.5% sodium chloride and 0.2% invert sugar. The formation of toxin is increased six-fold by the addition of 0.01 ml. of N/1 manganous chloride per litre of medium. Larger quantities decrease formation. The temperature limits of growth are 20° and 42°, optimum 34°; and limits of pH 5.2 to 8.9, optimum 7.0. The optimum pH for obtaining the toxin is 7.2 to 7.6 at 36°.—*J. chem. Soc. Abstr.*, i/1922, 795, 902.

References to the Use of Diphtheria Antitoxin

The earliest report of the use of the antitoxic serum (by Behring and Kossell) is found in the *Dtsch. med. Wschr.* of April 27th, 1893; this is noted in *Brit. med. J.*, i/1893, 83.

First English reported case by Eastes, 5 ml. of Aronson's preparation in a child of 10 years, with recovery.—*Brit. med. J.*, ii/1894, 125.

Diphtheria of the skin—the primary seat of infection being the eyes—thence to the vulva and the lower part of the face, has been satisfactorily treated with antitoxin.

Review of recent literature on diphtheria of vulva.—S. Veras, *Arch. Méc. Enf.*, 1932, Aug., 468.

In erysipelas the injection of diphtheria antitoxin in some cases causes rapid fall of temperature with disappearance of skin manifestations.

Diphtheria, malignant with multiple lesions, in a child 6 weeks old, failed to respond to 12,000 units of antitoxin.

In diphtheritic conjunctivitis, must be used early. If no response a mixed infection may be present.

The use of serum that possesses a high avidity for toxin (i.e. one that flocculates rapidly when it is mixed with toxin) advocated for the malignant type of diphtheria.—T. Madsen and S. Schmidt, *Z. Immunforsch.*, 1930, 115, 357.

No evidence of difference in therapeutic efficacy between concentrated and unconcentrated antitoxins, each containing about 900 units per ml.—*Rep. metrop. Asylums Bd.*, 1928-29.

Combined Use of Streptococcal and Diphtheria Antitoxins. Haemolytic streptococcus found in throat of 50% of diphtheria cases. Streptococcus antitoxin advocated in addition to diphtheria antitoxin.—F. Meyer, *Dtsch. med. Wschr.*, 1928, 215.

Combined use of streptococcus antitoxin early as means of preventing onset of septic symptoms.—F. von Borman, *Arch. Kinderheilk.*, i/1931, 241.

Bulk of evidence does not confirm value of combined use of streptococcus and diphtheria antitoxins.—A. Fleming and G. F. Petrie, "Recent Advances in Vaccine and Serum Therapy," 1934.

Failure of diphtheria antitoxin in some cases may be due to fact that diphtheria is sometimes wrongly diagnosed in cases of febrile angina where staphylococci and streptococci are present as well as *C. diphtheriae* to which the patient possesses a natural or acquired immunity.—H. Dold, *Dtsch. med. Wschr.*, 1927, 1760.

Combined Use of Insulin and Antitoxin. In febrile stage, carbohydrate metabolism is disturbed because of the toxæmia. Insulin treatment in conjunction with antitoxin gave reduced fatality rate.—E. C. Benn, E. Hughes, and S. Alstead, *Lancet*, i/1932, 281.

Patients experienced relief from physical distress by combined insulin and antitoxin.—H. E. de C. Woodcock, *Lancet*, ii/1932, 884.

Significance of sugar tolerance curves and value of insulin in toxic diphtheria discussed by N. D. Begg and E. H. R. Harries, *Lancet*, i/1935, 480. See also *Lancet*, i/1932, 281.

Diphtheria—review of.—*Rep. med. Res. Coun., Lond., 1923.*—*Brit. med. J.*, i/1924, 439.

Untoward Results, Serum Rashes, etc., with Diphtheria Antitoxin. The symptoms of diphtheria serum sickness are fever, rash, usually urticaria or a variety of erythema multiforme. Sometimes more unpleasant effects, namely pains in joints, tendons and fasciæ occur with fever.

Asthmatic patients should receive injections with caution, even as prophylactic.

Intense itching, subsequently vomiting, has been cured by 1/6 grain of morphine.

Attention drawn to the growing frequency of unpleasant reactions to the injection of diphtheria antitoxin. At one time these reactions were rare, now they occur in 80% of children and 95% of adults. Ephedrine by the mouth is successful in aborting these reactions—one tablet an hour before the injection and one tablet every 8 hours for the next fortnight. For children under 4, tablets contain 0.1 g.; between 4 and 9, 0.2 g.; and between 9 and 15, 0.3 g.—P. Paul Levy, *Brit. med. J.*, ii/1933, 354.

Diphtheria carriers are found of all ages and of either sex; the presence or absence of an obvious pathological condition is no criterion for detecting a carrier, of the length of carrier life, or of virulence. The length of carrier life seems to have no effect on virulence—bacilli have been demonstrated to be virulent after 4 to 8 months in the ear and nose of different individuals. Artificial immunisation under certain conditions may increase the number of virulent carriers, especially when only partially carried out in a community.

Of 1680 children with diphtheria, 86 showed hæmorrhages. Prognosis of epistaxis in concurrent faucial and nasal diphtheria is very serious, but epistaxis not a very grave sign in purely nasal diphtheria or when disease confined to tonsils or conjunctiva.—P. von Kiss, *Arch. Kinderheilk.*, ii/1933, 193.

Schick Test in Diphtheria (introduced by Prof. B. Schick, of Vienna, in 1913). Schick test toxin is injected into the skin to discover whether a person is immune or susceptible to diphtheria. If his blood contains antitoxin, so that he is immune, this antitoxin prevents the injected toxin from causing a skin reaction. If his blood contains no antitoxin, or insufficient for protection, a circumscribed area of redness about $\frac{1}{2}$ in. or 1 in. or more in diameter (which may not appear until the third day) persisting 7 to 10 days is produced, and on fading shows superficial scaling and persistent brownish pigmentation.

Schick Test Toxin. A standard diphtheria toxin is diluted so that 0.2 ml. contains the test dose. To ensure that the toxin injected is harmless, B.P. '32 requires that when it is diluted 50 times, 0.2 ml. must cause no reaction when injected into the skin of a guinea-pig, but when diluted 25 times, this dose must cause a reaction. Now the test toxin also contains toxoid which produces no skin reaction but combines with antitoxin. Tests are therefore required to ensure that the test toxin contains a normal amount of toxoid, neither unusually large nor unusually small. The first test requires that 1 ml. Schick toxin mixed with 1 ml. of a dilution containing 1/250th of a unit of antitoxin, must give a reaction on the skin of a guinea-pig when 0.2 ml. is injected. This test ensures that the amount of toxoid present is not unusually small, for, if it were, a person might appear immune who in fact had a very small amount of circulating antitoxin. The second test requires that 1 ml. of Schick toxin mixed with 1 ml. of a dilution containing 1/150th of a unit of antitoxin must give no reaction when 0.2 ml. is injected into the skin of a guinea-pig.

This test ensures that the amount of toxoid present is not unusually large, for, if it were, a person might appear susceptible who has a fair amount of circulating antitoxin. The second test requires that 1 ml. of Schick toxin mixed with 1 ml. of a dilution containing 1/150th of a unit of antitoxin must give no reaction when 0·2 ml. is injected into the skin of a guinea-pig. This test ensures that the amount of toxoid present is not unusually large, for, if it were, a person might appear susceptible who had a fair amount of circulating antitoxin. The diluting fluid may be either a sterile solution of sodium chloride, so that the diluted liquid is isotonic with the blood, or may be a sterile solution containing 1·5% *v/v* of a mixture of 57 g. of borax, 85 g. of boric acid and 99 g. of sodium chloride.

Method of Conducting the Test. 0·2 ml. of the standardised diluted diphtheria toxin is injected intracutaneously into the left forearm. A similar amount of control, i.e., toxin *which has been heated*, is injected into the right arm. A flush, sometimes with a deeper red centre, on the site of injection into the left arm, and the absence of an identical flush on the right arm indicate a positive reaction. This develops in from 24 to 72 hours and is more easily read on or after the third day.

The control test serves to eliminate *pseudo reactions* due to the presence in the test toxin of some substance which is more stable than the specific toxin and which causes reactions in sensitised individuals.

Immunisation. Patients who give a positive reaction should be immunised by *diphtheria prophylactic*, of which usually 3 injections of 1 ml. each are given at intervals of 7 to 10 days.

Babies up to 6 months seem to be immune; between the ages of 6 months and 5 years the majority give a positive reaction, and for children within these age limits the test is often considered unnecessary, and the children may be immunised without previous Schick testing. For immunisation one of the several forms of *diphtheria prophylactic* is used, the doses and the intervals varying with the different forms.

In school practice.—W. Dunn and co-workers, *Lancet*, i/1927, 178.

Diphtheria Prophylactic. The *B.P.* '32 has five forms of Diphtheria Prophylactic (*Toxinum Diphthericum Detoxicatum*) as follows:—

(a) **Diphtheria Toxin-Antitoxin Mixture**, prepared by adding diphtheria antitoxin to a filtrate of a culture on nutritive broth of *C. diphtheriæ*.

(b) **Diphtheria Toxoid** or **Anatoxin**, prepared by treating the filtrate with formaldehyde.

(c) **Diphtheria Toxoid-Antitoxin Mixture**, prepared by treating the filtrate with formaldehyde and adding a small quantity of diphtheria antitoxin.

(d) **Diphtheria Toxin-Antitoxin Floccules**, prepared by adding diphtheria antitoxin to the filtrate in the proportion necessary to produce suitable flocculation, separating the floccules and washing and suspending them in physiological solution of sodium chloride.

(e) **Diphtheria Toxoid-Antitoxin Floccules**, prepared by treating the filtrate with formaldehyde and then proceeding as for Toxin-Antitoxin Floccules.

Purified Diphtheria Toxoid. Culture filtrates containing toxins *treated with formaldehyde* are partially or completely converted into toxoids. The *Ramon flocculation test* being used for assaying strength of the fractions, the "*Langstaff dose*" being the amount of toxin equivalent to 1 unit of antitoxin by this test.—A. F. Watson and E. Langstaff, *Biochem. J.*, 1926, 763.

All forms of diphtheria prophylactic are submitted to a test to ensure freedom from toxicity which consists in injecting 5 ml. into each of 5 healthy guinea-pigs, and in seeing that none die within 6 days. Hence, 1 ml., which is the amount injected into a person, must contain less than one-fifth of the fatal dose for a guinea-pig. Further, if any of the guinea-pigs die later than 6 days, a second test is applied in which 1 ml. is injected into each of 5 more guinea-pigs. None of these guinea-pigs must die within 30 days. There are also tests to ensure efficiency. When a quantity not exceeding 5 ml. is injected into each of 10 normal guinea-pigs, these must be rendered immune in 6 weeks. The immunity may be tested in two ways; the Schick reaction may be performed, and 8 out of 10 must be found Schick-negative; or 5 lethal doses of diphtheria toxin may be injected into each of them, and 8 out of 10 must be unaffected by the injection.

Diphtheria toxin-antitoxin which was the original form of prophylactic used has been largely displaced by a preparation of diphtheria toxoid. Injections of toxin-antitoxin may be attended with some danger. Some fatalities have been ascribed to freezing of the mixture which destroys the antitoxin, leaving excess of the toxin. The toxin-antitoxin mixture should not be used after exposure to a temperature below 0°. The addition of formaldehyde renders the toxin non-toxic. (The anatoxin is stable for long periods below 20° and resists heating for 1 hour at 65° to 70°. —G. Ramon, *Ann. Inst. Pasteur*, 1925, 1, per *J. chem. Soc. Abstr.*, i/1925, 339. See also G. Ramon, *Brit. med. J. Epit.*, i/1924, 44.) It is not advisable to attempt immunisation in patients with advanced heart disease and kidney affection, or those recovering from acute infectious diseases. It is claimed that 70% to 90% of those treated are found to be immune after 8 weeks. From 1 to 5 years is the most favourable age for diphtheria prophylaxis.

References to Clinical use of Diphtheria Prophylactic

(a) **Diphtheria Toxin-antitoxin Mixture.** As already stated this has now largely been replaced by other forms of prophylactic. For references to its use see previous edition.

(b) **Diphtheria Toxoid or Anatoxin.**—Ministry of Health Memorandum 170/Med. Nov. 1932. Gives recommendations which are in accord with findings of conference of experts from different countries held in London,

in June 1931, under auspices of League of Nations. Some of recommendations are: At same time as Schick test a test for hypersensitiveness should be carried out by intradermal injection of a small dose of formol toxoid (0.2 ml. of a 1 in 100 or 1 in 200 dilution). Any reaction to this test within 24 to 48 hours should be taken into consideration when deciding method of immunisation. If no reaction greater than $\frac{1}{2}$ in. and no induration, immunisation may be carried out with formol-toxoid of 25 to 35 L.F. or greater strength in 3 doses at fortnightly intervals. If there is a reaction to the test with diluted formol toxoid, toxin-antitoxin floccules should be used as immunising agent in place of formol-toxoid. Immunisation should not be attempted in children under one year. Schick test should be repeated not less than 2 months after last immunising dose. If positive, whole immunising course should be repeated.

In a small number of cases injection of toxoid has been followed by reactions due to hypersensitiveness of the patient to certain proteins contained in the toxoid. These reactions are harmless to healthy persons and are rare in children under five. For older children test for hypersensitivity by intradermal injection of diluted toxoid—known as **Moloney test**. (*Vide* Min. of Health Memorandum above).

Use of the Moloney test makes it possible to immunise non-sensitive children with toxoid.—R. A. O'Brien and H. J. Parish, *Lancet*, ii/1932, 176.

Diphtheria, an almost preventable disease, still attacks some 40,000 people every year in England and kills 2,000. In a crucial test in the Edinburgh and Birmingham isolation hospitals immunisation virtually abolished diphtheria among the staff and the nurses, constantly and intensely exposed to risk.—W. T. Benson, *Edinb. med. J.*, May, 1934, 293, per *Brit. med. J.*, i/1934, 1081.

The intrinsic antigenic value of anatoxin should be of at least 5 antigenic units—that prepared by the Pasteur Institute is of 8 to 10 units. Initial injection subcutaneously 0.5 ml. After 3 weeks give a second injection of 1 ml., and 15 days later a third injection of 1 ml. to 1.5 ml. (this third injection is not always necessary). All children from 1 to 8 years should be vaccinated. In epidemics inject 1000 units of antitoxin preceded a few minutes by an injection of anatoxin, the second and third injections of anatoxin being given in the usual way. Nearly 300,000 persons vaccinated in France since 1926.—G. Ramon and G. I. Helie, *J. Amer. med. Ass.*, ii/1928, 1033.

Results of 1297 inoculations with diphtheria anatoxin.—*J. Amer. med. Ass.* ii/1925, 472.

After the first dose, 37% of children Schick-negative—after second dose 95% to 98% Schick-negative.—L. Marten, G. Loiseau and A. Lafaille, *Ann. Inst. Pasteur*, ii/1928, 959.

See also Tomesek, *Ann. Inst. Pasteur*, i/1932, 574, for results of inoculating 250,000 children in Hungary between 1930 and 1931.

Results in Canada: 400,000 people inoculated with toxoid between 1922 and 1927 without any untoward result.—J. G. Fitzgerald, *Ann. Inst. Pasteur* ii/1928, 1089.

Diphtheria toxoid (anatoxin) is a better immunising agent than toxin-antitoxin and may safely be employed in immunising adults. A first dose of 0.5 ml. is given, a second of 1 ml., and a third of 1 ml. to 1.5 ml., with an interval of 14 days between doses. If there is a marked "pseudo reaction" in the Schick test, or a history of diphtheria, give preliminary doses of 0.1 ml. to 0.25 ml. of toxoid.—G. F. Dick and G. H. Dick, *J. Amer. med. Ass.*, i/1929, 1903.

Diphtheria toxoid used for active immunisation without any undesirable local or general reactions. Sensitivity to toxoid demonstrated by intradermal tests. It should replace toxin-antitoxin.—Keller and Harris, *J. Amer. med. Ass.*, i/1934, 2163.

Diphtheria: Its Aetiology, Distribution, Transmission, and Prevention, by Graham Forbes (London, 1932), should be consulted for a full account of the subject.

"The evidence already available leaves no doubt that the disease and its often fatal consequences may now fairly be called avoidable."—J. Graham Forbes, *Spec. Rep. Ser. med. Res. Coun.*, Lond., No. 115, 1927.

(c) **Diphtheria Toxoid-antitoxin Mixture**. Should be employed on a national scale. More economical than treatment.—E. Donaldson, *Brit. med. J.* ii/1926, 551.

The permanence of the Schick-negative state. Of 440 Schick-positive children rendered negative by immunisation, 5% were found positive when re-tested 1 to 7 years later. All the "relapsed" individuals rapidly produced antitoxin in response to very small amounts of toxin and could be considered as being in a state of active immunity.—H. J. Parish, *Lancet*, ii/1928, 322.

(d) **Diphtheria Toxin-antitoxin Floccules.** The precipitate formed by mixing toxin and antitoxin in equivalent amounts contains all the specific antigen and antibody in the mixture with little non-specific matter.—P. Hartley, *Brit. J. exp. Pathol.*, 1925-6, 112. Owing to the elimination of much of the non-specific matter, the reaction following injection of floccules is less than that with toxin-antitoxin.

(e) **Diphtheria Toxoid-antitoxin Floccules.** Absolutely safe for immunisation of children.—A. T. Glenney and C. T. Pope, *J. Path. Bact.*, 1927, 587.

Immunity after the injection of floccules is said to develop rapidly.

Three injections may be needed. Little likely to produce reactions.—*Brit. med. J.*, i/1931, 757.

Rarely produces reaction in adults and practically never in children.—*Lancet*, i/1935, 229.

Satisfactory results obtained in adults.—D. J. Thomas and N. G. Howell, *Lancet*, i/1935, 579.

Alum Precipitated Toxoid. The addition of alum to toxoid to the extent of 0.2% provides a precipitate of high immunising power even in one dose, though it is apt to cause an annoying, but not harmful, reaction. Its use has been enthusiastically adopted in some of the Western and Southern States of the U.S.A., with a high conversion of Schick-positive children to negative after one dose.—*Brit. med. J.*, i/1934, 1081.

The precipitate produced by addition of alum to formol toxoid is used for immunisation against diphtheria in one dose of 0.5 ml. or 1 ml.

Superior to toxoid-antitoxin in the prevention of diphtheria. It induces immunity more rapidly and is the best antigen in epidemic periods when rapid induction of immunity is essential. The reactions are not more severe than those caused by toxoid-antitoxin. Observations based on treatment of 436 children with alum toxoid and over 7000 with toxoid-antitoxin.—J. C. Saunders, *Lancet*, ii/1932, 1047.

Slight and transient induration developed in approximately half of 38 cases treated and all the children known to be Schick-positive before treatment were negative when tested three months later. The rationale of alum-toxoid prophylaxis indicates that a certain amount of induration at the site of injection is to be expected. If it can be shown that this is transient the method seems to be well worth while, as the delayed absorption appears to have the effect of increasing enormously the antigenic response of the organism.—J. C. Saunders, *Lancet*, i/1933, 791.

One dose of alum precipitated toxoid rendered Schick-negative 92.4% of 185 strongly Schick-positive children of pre-school age. In another group of 613 children not previously Schick-tested, 96.6% were Schick-negative when tested 2 to 4 months after one injection.—Graham, Murphee and Gill, *J. Amer. med. Ass.*, i/1933, 1096.

No reactions other than an occasional slight induration observed in 135 infants immunised with one dose of alum precipitated toxoid.—Walker, *J. Amer. med. Ass.*, ii/1934, 227.

Results compare favourably with those following two doses of formol toxoid.—Kelber and Leathes, *J. Amer. med. Ass.*, ii/1934, 478.

Alum toxoid is slightly more effective than toxoid containing no alum.—White and Schlageter, *J. Amer. med. Ass.*, i/1934, 915.

By adsorption on aluminium hydroxide the purity of diphtheria toxoid is increased 150 times. Tests on 9,000 persons show that the addition of aluminium hydroxide increases immunising power and practically no reaction is produced.—S. Schmidt, *Dansk Tidsskr. Farm.*, 1933, 123, per *Quart. J. Pharm.*, 1934, 152.

Passive immunity to diphtheria was obtained in 97.9% of all cases and 100% under 10 years in a series of 100 Schick-positives by the injection of 500 units of diphtheria antitoxin, the duration of immunity being from 14 to 21 days.—E. G. Munro Jones and J. W. Kershaw *Brit. med. J.*, ii/1933, 970.

Dysentery. There are two main types of dysentery—Amœbic and Bacillary (*cf. Vol. I*, pp. 519, 912).

Characteristics of *Entamœba histolytica*. The entamœba varies in size from 6 to 35 μ , though usually about 12 to 24 μ . Red blood corpuscles, bacteria, cells, etc., may often be seen in the interior though the ingestion of red corpuscles is by no means a constant factor. The organism can, according to Rogers, only rarely be found in pus, but is always present in scrapings from the wall of the abscess. The amœba passes through the intestinal wall and on reaching the submucous layer forms an abscess. Hewlett says the organism may be cultivated on ordinary agar if an organism, e.g. *B. coli*, be present. For a description of this and other amœbæ see Medical Research Com. *Brit. med. J.*, i/1917, 609; also H. A. Haig, *Lancet*, ii/1919, 823; and J. S. White, *Pharm. J.*, i/1915, 797.

To Search Stools and Mucus for *Entamœba Histolytica*. In searching mucus for amœbæ stain with a little methylene blue and examine with low power, e.g., $\frac{1}{2}$ in.—turn on the $\frac{1}{8}$ in. to verify.

Alternatively, place a small piece of freshly passed stool on a slide, adding one or two drops of 1 in 10,000 neutral red in normal saline. Examine with $\frac{1}{8}$ in. objective. The amœbæ take up the neutral red, all other constituents of the fæces, even the leucocytes, remaining uncoloured.

Cultivation. 10 g. of specimen is shaken with 100 ml. of saline in a mechanical shaker 5 minutes and poured on a fine silk of mesh 40 μ stretched on a tambour. It is gently stirred with a rod and the filtrate or a portion of it is centrifuged one minute at 1200 revolutions per minute, the supernatant liquid poured off and the volume made up again with normal saline. Shake and again centrifuge. Repeat until the supernatant liquor is almost clear. Finally shake the deposit with 10 ml. normal saline and allow to stand for 10 minutes. The upper portion is then poured off and thoroughly centrifuged, and loopfuls used for making hanging-drop preparations for cultivation. For counting, Bottcher's slides are used.—*Lancet*, i/1917, 179.

No purgative should have been given for some days, otherwise the precystic forms, difficult to identify, will be present. Examination during emetic administration is useless.

For amœbæ mix a small piece of mucus with normal saline and examine unstained under $\frac{1}{8}$ in. objective.

For cysts and precystic forms emulsify a little of the stool (1) with saline and (2) with 1% aqueous solution of iodine in potassium iodide.

E. histolytica cultivated by Bœck and Drbohlav. In culture, *E. histolytica* feeds on bacteria and red blood cells whenever the latter are present in the medium.—*J. Amer. med. Ass.*, ii/1925, 196. See also *Amer. J. Hyg.*, 1924; *Lancet*, ii/1926, 762; and *Yearb. Pharm.*, 1927, 79; and detection in fæces *ibid.*, 80, 371.

Viability of cysts of *E. histolytica* studied by keeping them in an ice-box and subculturing at intervals; they were viable up to 46 days. Subcultures of Dobell's strains survived under variable conditions of temperature, etc., up to 27 days.—T. and V. Wright, *J. trop. Med. (Hyg.)*, ii/1932, 337.

Method for counting *E. histolytica* *in vitro* with hæmocytometer.—M. Paulson, *J. trop. Med. (Hyg.)*, i/1933, 109.

Diagnosis. A method of concentration of cysts from stools: Shake a lump of fæces (at least 1 g.) in about 30 ml. of normal saline preferably with a mechanical shaker in a large flask or bottle for $\frac{1}{2}$ hour. Then transfer to a separating funnel and shake by hand for $\frac{1}{2}$ minute with 10% or 20% of its volume of ether. Allow to stand for a minute or two. The cysts remain in the saline, fæcal debris rising in a mass at the top of the saline, immediately below the excess of ether. The saline is removed and centrifuged. The sediment in the centrifuge tubes would be some 15 times as rich in cysts as the original matter. If desired this can be again shaken up and centrifuged afresh.—J. W. Cropper and R. W. H. Row, *Lancet*, i/1917, 179.

In diagnosis of chronic dysentery by means of the sigmoidoscope the large bowel is emptied by means of $\frac{1}{2}$ ounce of castor oil in the evening, followed next morning by a soap and water enema, immediately after which 15 minims of tincture of opium is given. The distance the instrument can travel varies—up to 12 in. has been passed.—P. Manson-Bahr and A. L. Gregg, *Trop. Dis. Bull.*, 1921, 35.

The diagnosis of intestinal amœbiasis assisted by provoking an artificial relapse with keratin-coated capsules of bile extract, 0.2 g., 3 after each meal. The stools become fluid and organisms and cysts observed in large numbers.—Le Noir and de Fossey, per *Trop. Dis. Bull.*, 1922, 688.

Entamœba coli. Syn. Amœba coli of Losch. Occurs in the upper part of the large intestine. It appears to be harmless. According to Schaudin it differs from *E. histolytica* in that the ectoplasm is not distinctly seen except during the formation of a pseudopodium and the nucleus stains deeply. It never takes up red cells. *E. coli* multiplies by binary fission and also by multiple fission into 8 small amœbæ. *E. histolytica* produces an indefinite number of small amœbæ.—J. S. White, *Pharm. J.*, i/1915, 797. For further differences see *E. histolytica*.

Comparison of *E. histolytica* with *E. Coli*.—The following table shows differences from *E. coli*, which is so commonly found in fæces. Actual measurement of size is a great help. Amœbic diarrhœa should never be diagnosed on precystic forms alone.

	<i>E. histolytica.</i>	<i>E. coli.</i>
Active forms	Size 20μ to 30μ . Clear ectoplasm, granular endoplasm Red blood cells included Sudden explosive movements Eccentric inconspicuous spherical nucleus with small central dot.	Size 20μ to 30μ . Ectoplasm and endoplasm both granular Bacteria, yeasts, vegetable cells included Movements very slow and no locomotion Central conspicuous nucleus with an eccentric dot.
Pre-cystic forms	Size 7μ to 14μ Round. Ectoplasm and endoplasm not differentiated No inclusions No movements Nucleus a beaded ring. May be elongated and undergoing division.	Almost impossible to distinguish from <i>E. histolytica</i> .
Cysts	Size 7μ to 9μ , or 11μ to 14μ . 1, 2 or 4 nuclei Mature cyst has 4 nuclei Mature cyst contains glycogen.	Size 15μ to 20μ . 1 to 8 nuclei Mature cyst has 8 nuclei Mature cyst contains no glycogen.

Many cases of diarrhœa or colitis might be found to be amœbic in origin if the stools were systematically examined.—L. E. H. Whitby, *Midx. Hosp. J.*, March, 1925.

Entamæba Nana (Wenyon and O'Connor) inhabits the human intestines, in addition to *E. coli* and *E. histolytica*. *E. Nana* is a small amœba measuring when rounded 6 to 12 μ . The cysts are very resistant. No evidence that it is pathogenic.—C. Dobell and Margaret W. Jepps, *Brit. med. J.*, i/1917, 607.

Councilmania lafleuri, an amœba of man, has clear pseudopodia, eats red blood corpuscles and has a very marked resemblance to the motile forms of the amœbæ of dysentery. Its cysts have 8 nuclei resembling those of *E. coli*, but differ from them in the larger subdivided central karyosome of the nucleus. It is wholly resistant to all forms of emetine treatment and as it often occurs coincidentally with the amœbæ of dysentery and persists after the extermination of the dysenteric infection it might give a misleading picture of the failure to cure by the emetine treatment. Presence invariably revealed by its characteristic cysts but motile stage separated with difficulty from that of *E. dysenteriae*.—C. A. Kofoed, *Int. Conf. Trop. Amer.*, 1924, 327.

***Bacillus Dysenteriae*.** The dysentery organisms are divisible into two main groups. According to a Medical Research Committee Report, *B. dysenteriae* (Shiga) and *B. dysenteriae* (Flexner), it is universally agreed, cause bacillary dysentery. They occur as short rods, destitute of flagella, and non-motile, gram-negative, fermenting glucose without gas formation and producing alkalinity in milk.

Shiga's organism is relatively well defined. It does not ferment mannite, and does not produce indole in peptone water. It is highly toxic to man and animals. It is a distinct and separate species. The Flexner group produces acid in mannite and + or — indole in peptone water.

Flexner's, however, is separable into several distinct strains. Details.—F. W. Andrewes, and A. C. Inman, *Serological Races of the Flexner Group*, *Spec. Rep. Ser. med. Res. Council Lond.*, No. 42, 1920; *Lancet*, i/1920, 162; see also *ibid.*, i/1918, 560.

The bacilli of Shiga and Flexner are non-motile, non-spore-forming, do not stain by Gram's method and grow on all ordinary media. In cultural characters they resemble *B. coli communis*.

The dysentery bacilli have an exotoxin and endotoxin. The former is a neurotoxin; the latter acts as a poison on the intestine. By the suppression through anaerobiosis of the exotoxin-producing activity of *B. dysenteriae* Shiga, a pure endotoxin is produced directly from the culture.—J. E. McCartney and P. K. Olitsky, *per J. trop. Med. (Hyg.)*, 1923, 259.

Serum diagnosis of chronic bacillary dysentery. Standard agglutination tests with Shiga-Flexner groups of dysentery cultures may have large field of usefulness in helping to determine prevailing type of infection, allowing of treatment by dysenteric vaccines, made up of organisms corresponding to prevailing type (Thomson's Detoxicated Vaccines). Standard agglutination tests may possibly be of value even in diagnosis of chronic dysentery.—E. H. R. Altounyan, *Lancet*, i/1924, 75.

Differential Diagnosis of Amœbic and Bacillary Dysentery. It is not always easy to find *E. histolytica* in the stools of early amœbic dysentery, but if pseudopyknotic nuclei are present the diagnosis is certain. It is confirmed by the detection of Charcot-Leyden crystals and eosinophils, though these do not develop quite so early.—A. Alexieff, *per Lancet*, ii/1932, 854.

Characteristic cellular exudate in the stools of amœbic and in bacillary dysentery. The finding of *E. histolytica* in the midst of a "bacillary" exudate of this kind indicates that a double infection is present, although attempts to

isolate dysentery bacilli may fail.—J. G. Willmore and C. H. Shearman, *Lancet*, i/1918, 200. See also G. M. Findlay, *Lancet*, i/1919, 135.

Notes on ætiology of dysentery. *E. histolytica* in 63 cases out of 217, and *B. dysenteriae* (Shiga) in 47.—C. J. Martin, *Brit. med. J.*, i/1917, 479.

According to the *Annual Report on the Health of the Army* for 1925, nearly all the cases of dysentery in Iraq were amœbic, whereas only one of the cases in Turkey was of that type, and in Egypt 35 out of 64 cases were amœbic. *Brit. med. J.*, i/1926, 202; K. Boney queries these figures.—*ibid.*, 303.

Antidysentery Serum (Shiga)

Standard. The international standard is a quantity of dried serum kept in the Serum Institute in Copenhagen. The British standard, which has been carefully compared with the International Standard, is kept in the National Institute for Medical Research, Hampstead.

Unit. The International Unit is the activity in a fixed weight of the International Standard.

Method of Standardisation. A preparation corresponding to a test toxin is first made. A toxin is, however, by definition a poisonous substance liberated in a culture medium by a growing organism, and the preparation made from *B. dysenteriae* (Shiga) is not always a toxin in this sense. It may be a bacillary emulsion, prepared by growing a smooth strain of a highly toxigenic *B. dysenteriae* on nutrient agar for 48 hours at 37°. The growth is washed off the medium and the suspension is killed by heating to 56° for 15 minutes and then centrifuged to collect the dead bacilli. These are dried *in vacuo* over P₂O₅, and ground to a powder. The test toxin may also be a broth filtrate prepared by growing the bacillus in alkaline broth at 37° for 2 or 3 weeks. The broth is sterilised by filtration, and the toxin is precipitated by adding 40 g. of ammonium sulphate to each 100 ml. The precipitate is again dried *in vacuo*. Finally, a purified toxin may be prepared by dialysing the sterilised broth filtrate under pressure against water. The reaction is then adjusted to the isoelectric point to precipitate the toxin which is collected and dried.

When the toxin is prepared the test dose is determined; this is the dose which when mixed with 1 unit of standard antitoxin causes the death of one half of a group of mice injected with it; a suitable toxin has a test dose which is not less than 20 average lethal doses. Unknown samples of antitoxin are then estimated by mixing different volumes with the test dose of the toxin. These mixtures are injected into groups of mice, and the mixture which kills half of a group of 30 mice contains an amount of antitoxin equal to 1 unit.

Dysentery Anatoxin. The preparation and use of.—*Ann. Inst. Pasteur*, i/1926, 134, per *Prescriber*, Jan., 1927, 16.

ANTI-DYSENTERY BACTERIOPHAGE. Encouraging results with, in bacillary dysentery—70% of cases gave rapid improvement.—A. Compton, *Lancet*, ii/1929, 275.

Bacteriophage said to have effected a speedy cure in 30% of cases but very little effect in remainder.—T. H. McCay, *Indian med. Gaz.*, 1932, 666.

Metadysentery is due to a group of bacilli including *B. metadysentericus*, *B. ceylonensis* and others. True dysenteric symptoms are usually lacking. The patient feels tired, nervy, and complains of flatulence with occasional diarrhœa.

followed by long periods of constipation. Diagnosis based on presence in the blood of specific agglutinins and on repeated bacteriological examination of stools. A bacteriological description of the group is given in *Amer. J. trop. Med.*, July 1927.—Sir A. Castellani, *Lancet*, ii/1929, 372.

Bacillus metadysentericus (Castellani)—virulence of. Results of experiments on rabbits. Its virulence is less marked than that of *B. Shiga-Krusel* while having an apparently similar toxin. Resistant to direct sunlight for $1\frac{1}{2}$ to 2 hours, and still alive after 6 hours' exposure to diffused light.—G. Olivi, *J. trop. Med. (Hyg.)*, 1923, 123.

In colitis a new bacillus found constituting a third group of dysentery bacilli. Pathogenic for man and animals. Easily confused bacteriologically with Flexner-Y type, but slow fermenter of lactose.—S. W. Patterson, per *J. trop. Med. (Hyg.)*, 1923, 64.

Flagellate Dysentery. A survey of the literature of flagellate dysenteries it is stated, leaves the mind of the reader in a turmoil as to their pathogenicity or otherwise. Few admit the presence of flagellates in the bowel as anything more than a coincidence, when found along with dysenteric symptoms. Others credit *Lamblia intestinalis* with pathogenic effects and still leave *Trichomonas intestinalis* and *Chilomastix mesnili* in the coincidence group. An analysis of 716 cases showing these and other infections. Purgation, thymol, emetine, bismuth iodide and colon lavage valuable. Flagellate dysentery can be cured in at least 50% of cases.—H. G. Whittingham, *Brit. med. J.*, i/1923, 799.

Giardia lamblia, *Trichomonas hominis* and *Chilomastix mesnili* are probably the real ætiological factors of "flagellate diarrhœa." Carnivorous animals are rarely infected with intestinal protozoa; a carnivorous diet is unfavourable to giardias and trichomonads of rats, and such a diet may also be unfavourable to these flagellates in man. Diarrhœic patients so treated have shown either an extremely marked diminution in the number of flagellates or a total riddance of them.—R. W. Hegner, *Int. Conf. Trop. Amer.*, 1924, 404.

These parasites are very troublesome to remove. The best results were obtained with betanaphthol 15 grains and bismuth salicylate 20 grains thrice daily. Turpentine in 10 minim doses tried but not so useful.—*Brit. med. J.* ii/1916, 407.

Dysentery Carriers (see also Vol. I, pp. 521, 1047).—Healthy carriers are very rare and of no importance. Actual carriers are to be found among the incomplete convalescents who form a high percentage of the cases. In combating an epidemic it is necessary to reduce as far as possible the number of such cases and to isolate very strictly those that are already of this type.

There are said to be nearly two million *E. histolytica* cyst-passers in England.—*Lancet*, ii/1926, 762.

The spread and incidence of protozoal infections in the population of this country. As the result of examination of nearly 3000 people, including army recruits, adult civilians, children under 12, and asylum patients (none of whom had been out of England, with the exception of a very small percentage in the last group), *E. histolytica* was found in every section of the population, establishing the wide occurrence of the infection in this country, and showing that it is no longer necessary to presume foreign origin for any home case of amœbic dysentery or for any infection with *E. histolytica*. Indigenous cases of acute amœbic dysentery do occur in England and may be more common than has been supposed—possibly concealed under such names as "hepatitis" or "ulcerative colitis."—A. Malins Smith, *Brit. med. J.*, ii/1924, 897.

Systemic infections by *E. dysenteriae*. From its portal of entry through the epithelium of the colon into the submucosa, *E. dysenteriae* tends to spread in the margins of ulcers of the colon into capillaries and smaller veins and thence may make its way into the capillary net of the liver, through the heart to the capillary net of the lung, and thence to the systemic circulation. Liver, lung and brain abscesses are thus interpreted as hæmatogenous invasions by way of the blood stream—as is also infection of bone-marrow. Following the finding of *E. dysenteriae* in the stools of 18 out of 20 cases of Hodgkin's disease, the authors infer that this disease is amœbiasis of the lymphatic system, the amœbæ arriving at these locations by the systemic circulation, or possibly the lymphatic system. Resistant cysts discharged in the fæces the sole mode of infection, the agencies causing contamination being flies and the soiled hands of food-handlers.—C. A. Kofoed and co-workers, *Int. Conf. Trop. Amer.* 1924, 381-397

Epidemic encephalitis (previously called **Encephalitis lethargica**). The disease shows marked resemblance to acute poliomyelitis in methods of infection and general behaviour. Whilst the view is held that acute poliomyelitis, cerebrospinal fever, and encephalitis lethargica are independent entities, the resemblances indicate that they belong to the same epidemiological family tree and the study of one may elucidate the nature of the others.—A. S. MacNalty, *Lancet*, i/1925, 594.

Infection may be due to the damaging of the nasal mucous membrane by a catarrhal organism, so that when inhaled the virus of encephalitis passes through and is absorbed into the brain via the perineural lymphatics.—A. L. Yates and S. Barnes, *Lancet*, ii/1925, 130.

5000 cases were reported in England and Wales in 1924 and 1025 in 1923. A large number of mild cases pass unrecognised—a truer estimate for 1924 would probably be about 50,000. Mortality statistics taken from recent Ministry of Health Reports are as follows:—1930, 916; 1931, 962; 1932, 825; 1933, 815.

Parkinsonism, a form of paralysis agitans, is a common sequel even in young children—characterised by rigidity of musculature of body, the face becoming devoid of expression, and the speech affected; as the stiffness increases the patient becomes unable to feed or dress himself and finally may become bedridden. Further sequelæ are neurasthenia, intractable insomnia and disturbances in respiratory mechanism. Moral degeneration often follows the disease. The causal organism is a filter-passing virus. Symptoms sometimes like influenza, for which it is often diagnosed. Sleeplessness, restlessness, derangement of vision, severe pains, incessant hiccough or tendency to sleepiness may be symptoms of acute attack.

Treatment: Intraspinal injections of autoserum gave good results in epidemic encephalitis.—per *J. Amer. med. Ass.*, ii/1925, 1095.

Patients may recover from the severe acute attacks, from the respiratory symptoms and from behaviour and other residual sequelæ, but rarely, if ever, from the Parkinsonian syndrome.—L. H. Ziegler, *J. Amer. med. Ass.*, ii/1928, 141.

The only drugs still spoken of favourably when used for palliative purposes in certain phases of the chronic conditions are atropine and its derivatives, bulbocapnine, hyoscine (scopolamine), and stramonium.—Second Report by the Matheson Committee, New York, *Brit. med. J.*, ii/1932, 247.

Tolerance to atropine in these cases exceptionally great, tending to increase with severity of disease, though in acute stage it has no special action. While ordinary doses of atropine act only on the nervous system, in large doses it acts on those parts of the peripheral central nervous system involved in lethargic encephalitis. Dosage begins with 1 drop thrice daily of 0.5% solution, doubled on the second day, trebled on the third and increased by 1 drop daily till the 10th day, then every other day by 1 drop, up to 20 drops thrice daily, then every third day till optimal dosage is reached, i.e., when no further improvement of symptoms is noted, when it is decreased by 1 drop twice a day till old symptoms begin to reappear when process is reversed and dosage increased again, the treatment requiring 3 months on the average. Dryness of throat no indication for stopping increase as with a further increase this symptom usually disappears, but if giddiness, palpitation, and gastric disturbances occur stop increasing for a few days. Encouraging results in 104 cases.—G. Kinberg, per *Brit. med. J. Epit.*, ii/1933, 2.

A classification of the methods of treating epidemic encephalitis.—J. H. Neal and I. A. Bentley, *Arch. Neurol. Psychiat., Lond.*, 1932, 28, 897.

See also Vol. I, p. 1050, and *Poliomyelitis*, this Vol., p. 582.

Filariasis. In *Filaria sanguinis hominis* infection, or elephantiasis, larvæ only of *Filaria* occur in the blood. The worm itself is subcutaneous. *C. quinquefasciatus*, *Aedes variegatus* and *A. albopictus*, *Anopheles rossi*, *Anoph. ludlowi* and *Anoph. costalis* are proven vectors. Sheathed embryos of the filaria are taken up by *Culex*, and the larvæ in due course reach the definitive host (man) through the intact pores of the skin (Bahr).

The female adult worm was discovered by Bancroft, the male by Aranjol and the embryo by Demarquay and Lewis.

Enumeration of Filarial Diseases. The diseases known to be produced by or associated with *F. bancrofti* are: abscess, lymphangitis, arthritis, synovitis, abscess of hip-joint, varicose groin-glands, varicose axillary glands, lympho-scrotum, cutaneous and deep lymphatic varix, orchitis, funiculitis, chyluria, elephantiasis of the leg, scrotum, vulva, arm, mamma and other parts, chylous dropsy of the tunica vaginalis, chylous ascites, chylous diarrhoea, and probably other forms of disease depending on obstruction or varicosity of the lymphatics or on the death or injury of the parent filariæ in a lymphatic abscess—including fatal peritonitis and secondary infections by pyogenic micro-organisms.—Manson's *Tropical Diseases*, 1929.

Mechanical basis of periodicity in *Wucheria Bancrofti* infection.—Lt.-Col. Clayton Lane, *Lancet*, ii/1933, 399.

Filariasis (*F. bancrofti* infection), with plenty of embryos present in the night blood, treated with antimony tartrate intravenously—no effect (contrary to Rogers).—G. C. Low and A. L. Gregg, *Lancet*, ii/1920, 551.

Carbon tetrachloride intravenously and intramuscularly has been tried on animals and suggested in loa-loa.—S. Adler, *Ann. trop. Med. Parasit.*, Oct. 1923.

The "Blinding Filaria" of Guatemala (*Onchocerca cæcutiens*, Brumpt, 1919).—F. Fülleborn, *Int. Conf. Trop. Amer.*, 24, 241-255.

Gas Gangrene. Gas gangrene is caused by *B. Welchii* (syn. *B. ærogenes capsulatus*, *B. perfringens* or Fraenkel's bacillus)—the bacillus of Welch—often in association with other organisms such as *B. œdematis maligni* (*Vibrion septique*) and *B. novæ* (*B. œdematiens*). Gas gangrene infections were common during the War owing to infection of wounds with soil, clothing, etc.

They are not altogether uncommon in civil practice; they occur in cases of compound fractures, crushed wounds, and wounds containing foreign bodies, bits of clothing, soil, etc.; also as a complication after appendicectomy.

In Great Britain at the present time *B. Welchii* is by far the commonest of the three organisms, and it is questionable if an account need be taken of its associates when considering the preparation of a specific serum for treatment.—A. Fleming and G. F. Petrie, *Recent Advances in Vaccines and Serum Therapy*, London, 1934.

Bacteriology. Sir A. E. Wright and his co-workers conclude that the growth of *B. Welchii* does not necessarily turn on the presence or absence of oxygen, but rather on a mechanical factor which appears to be the presence of some hole to serve as a nidus in which the microbe can concentrate its chemical effort at first upon a fractional portion of the culture medium.

B. Welchii, though usually considered an anaerobe, will grow freely in open narrow tubes. It grows vigorously in liquid medium when nitrogen containing 1% oxygen is bubbled continuously through the tubes, but it is inhibited by higher proportions of oxygen.—C. G. L. Wolf, C. M. McGill and J. E. G. Harris, *Lancet*, ii/1917, 787.

The *B. Welchii* is a normal inhabitant of the intestines of adults and is found sometimes in small numbers in the stools of infants. If in excessive numbers, and if the diet contains an undue amount of fermentable carbohydrate, diarrhoea is likely to result.—J. P. Symonds, *Monogr. Rockefeller Inst. med. Res.*, Sept. 27, 1915; *Brit. med. J.*, i/1916, 102.

B. aerogenes capsulatus, *B. œdematis maligni* and *B. tetani* isolated from gangrenous wounds. Morphology. Staining reactions.—H. R. Dean and T. B. Monat, *Brit. med. J.*, i/1916, 77.

Infection of wounds by gas-producing organisms—either that of malignant œdema or by *B. aerogenes*.—A. Mackenzie Forbes, *Brit. med. J.*, i/1916, 369.

Natural history of septic wounds—an exhaustive paper. Preponderance of anærobic organisms: *B. œdematis maligni*, *B. perfringens* and *B. Hibler*. Small incidence of *B. tetani*. The wounded tissues contain anaerobes months after the original injury. The activity of the anaerobes depends to a great extent on their symbiosis with aerobes.—Sir K. Goadby, *Lancet*, ii/1916, 89.

Gas-gangrene Antitoxin (*Perfringens*)

Standard. There is an international standard kept in the Serum Institute at Copenhagen which is a quantity of dried gas-gangrene antitoxin and a British standard kept in the National Institute for Medical Research.

Unit. The unit is the activity contained in a given quantity of the international standard; the weight of the British standard which contains 1 unit has been determined by careful comparison.

Method of Comparison. A test toxin is prepared by growing *B. Welchii* for 16 hours; the medium is sterilised by filtration and ammonium sulphate is added until a precipitate is formed which is collected and dried. The test dose of the test toxin is determined by finding what amount of the test toxin, mixed with 0.2 unit of standard antitoxin, kills some but not all of a group of mice into which it is injected intravenously. Unknown samples of antitoxin are then assayed by making mixtures of different volumes with the test dose of the test toxin. These mixtures are then injected into mice, and the one which kills some but not all of the mice contains an amount of antitoxin equal to 0.2 unit.

Gas-gangrene Antitoxin (*Vibrio Septique*)

Standard. There is an international standard kept in the Serum Institute at Copenhagen, and the unit is defined in terms of this standard, the unit being the antitoxic activity present in a given weight. The method of estimating unknown samples of antitoxin is similar to that described for *B. Welchii* antitoxin, and consists in preparing a test toxin of which the test dose is carefully determined in one of two ways, either by intravenous injection into mice or by intracutaneous injection into guinea-pigs. The test dose is the least amount of toxin which mixed with 1 unit of antitoxin kills some but not all of the mice which receive it; alternatively it is the least amount which mixed with 0.5 unit of antitoxin causes a reaction in the skin of the guinea-pig. When the test dose is determined by one of these methods, unknown samples of antitoxin are estimated by the same method. Thus the quantity of antitoxin is determined which when mixed with one test dose of the test toxin kills some but not all of the mice which receive it. This quantity of antitoxin is 1 unit.

References to Clinical use of Gas-gangrene Antitoxin

Intestinal Obstruction. Toxæmia in primary acute intestinal obstruction and in peritonitis with obstruction, due to absorption of the toxin of gas-forming organisms, especially *B. Welchii*. Alkaline contents of lower portion of small bowel, when it is paralysed or obstructed, provide requisite anaerobic conditions for proliferation of *B. Welchii*. Improvement recorded in patients suffering from peritonitis with paralytic obstruction by treatment with *B. Welchii* antitoxin. In 54 cases of acute intestinal obstruction treated with antitoxin mortality rate was 9.3% as compared with 24.8% in cases not treated with antitoxin. In 256 cases of acute appendicitis treated with antitoxin mortality rate was 1.2% as compared with 6.3% in control cases.—B. W. Williams, *Lancet*, i/1927, 907; and *Brit. J. Surg.*, 1926, 54.

B. Welchii serum of real value when gangrenous bowel has to be dealt with but of no benefit in straightforward cases of simple obstruction.—D. P. C. Wilkie, *Brit. med. J.*, ii/1932, 545.

Puerperal Sepsis. A. J. Wrigley (*Proc. R. Soc. Med.*, 1930, 1643) comments on incidence of *B. Welchii* infections during pregnancy and the puerperium as shown by records of Obstetrical Dept., St. Thomas's Hospital, London. During years 1922-27, of 16 deaths from puerperal sepsis and generalised gas gangrene the bacillus was found post-mortem in 6. *B. Welchii* not present in cervix before delivery nor in lochia after delivery when pregnancy, labour and puerperium are normal, but of 69 cases in which these were abnormal *B. Welchii* was isolated in 13. Gas-gangrene antitoxin should be given early in all cases presenting circumstances which may lead to generalised infection without waiting for bacteriological confirmation of the presence of anaerobic organisms.

Recovery in a case of puerperal infection treated with antistreptococcus serum, gas-gangrene antitoxin and anticoli serum.—F. Ivens, *Lancet*, i/1929, 606.

Details of a case of gas gangrene infection in a woman who died during parturition.—J. and P. Adams, *Brit. med. J.*, ii/1931, 1179.

Wounds. Every crushed or lacerated wound is a potential source of gas gangrene especially if contaminated with foreign bodies. Warning signals are sudden high temperature, or temperature mounting a degree or two each day with rapid pulse and, in young patients, rapid respirations; intense pain. Early signs are the toxic appearance of patient, gangrene of lacerated skin and copper colour of wound. Use of polyvalent gas-gangrene antitoxin together with tetanus antitoxin advised in all cases showing suspicion of gas gangrene.—M. Wiseberg, *Canad. med. Ass. J.*, ii/1932, 278.

A mild vaccine of sensitised polyvalent *Streptococcus* 5 million, with *B. proteus* 10 million, to be given pending bacteriological report. In case of gas gangrene *Strepto.* vaccine combined with *B. proteus* and *B. lactis aerogenes* to be given—10 million each—repeated on the third day.—Sir K. Goadby, *Lancet*, ii/1916, 585.

Eusol has been employed in the treatment of gas gangrene (Vol. I., p. 42) see also quinine hydrochloride, Vol. I, p. 721.

B. tumefaciens, a pathogenic anaerobe, isolated from a case of gas gangrene; an actively motile, gram-positive bacillus, resembling *Vibrion septique* in morphological characters but easier to cultivate and forming spores with great facility. The lesions produced resemble those of *Vibrion septique* in being hæmorrhagic.—W. J. Wilson, *Lancet*, i/1919, 657.

B. sporogenes. This organism differs from the gas bacillus (*B. Welchii*) and the *Vibrion septique* in being actively proteolytic, whereas the latter act on carbohydrates rather than on proteins. Next to the gas bacillus it was the organism most frequently encountered in war wounds and was regarded as the main cause of their foul odour. Like the gas bacillus, it is often found in human or animal fæces and in fertilised soils.

It is a bacillus with rounded ends ($5 \times 0.8\mu$), actively motile, and gram positive; it liquefies gelatin and digests blood serum. It does not seem to be pathogenic but appears to exalt the virulence of the gas bacillus.

It is a common contaminant of other anaerobic cultures and since its spores are highly resistant it is difficult to separate it from others. Metchnikoff's organism, the Reading bacillus, *Bacillus XI*, and—by some—Koch's organism of malignant œdema are regarded as identical with *B. sporogenes*.—Stitt.

Braxy. This disease in sheep is an example of a pure infection with an anaerobe—a stomach infection. An injury due to the lowering of the tissue defences from chills, frosted food, etc. The anaerobe invades the system in pure culture. In braxy, had it been known during the war, is to be found one of the most important of the gas gangrene organisms; other anaerobes and aerobes are left behind in the invasion—a natural purification of the bacillus by animal passage. Anaerobic infections, from the war standpoint, are of extreme importance.—Prof. S. H. Gaiger, *Brit. med. J.*, ii/1922, 962.

Animals can be immunised by inoculation with the toxin of *Vibrion septique* or with a mixture of toxin and antitoxin. It is more usual, however, to use formalised cultures of *V. septique*.

By inoculation with one dose of formal-culture, the mortality from braxy in sheep was reduced to 1.4%, compared with 9.4% in uninoculated animals.—W. L. Stewart, *Vet. J.*, 1929, 400.

Glanders. Mallein. A growth of the glanders bacillus in glycerinated broth, corresponding in mode of preparation to Koch's original tuberculin. This vaccine is used as a test for the presence of glanders in sick horses, and has been injected for the cure of chronic glanders in man. The mallein of the Lister Institute for animals is injected in doses of 1 ml. for diagnostic use subcutaneously in the neck over vertebræ about midway between jaw and shoulder; complete reaction is a rise in temperature of 2.7°F. after 12 to 20 hours and an extensive hot and painful local swelling.

Should the rise in temperature not exceed 1°C. or 1.8°F. , or the size of the swelling not exceed 3 in. in diameter in 24 hours, the freedom of the animal from glanders is highly probable.

The temperature reaction is unreliable in all cases in which the temperature at the time of inoculation is 2.5°F. above normal. In such cases, if there are any suspicious clinical signs to assist, reliance may be placed on the occurrence of the local swelling.

Human Glanders. Mallein satisfactorily employed in dose of 10 to 15 minims. Difficulty of diagnosis owing to close resemblance between the ulceration and the tertiary syphilitic ulceration of the buccal and pharyngeal cavities.—*Brit. med. J.*, i/1909, 319.

A fatal case.—*Lancet*, ii/1902, 941.

Intradermo-palpebral test is the most popular. Watson and Heath (America) have shown that the horse can be hyper-immunised by repeated inoculations of Mallein, and several very serious human cases have been treated with the serum in Canada with dramatic results.—*Brit. med. J.*, ii/1924, 530.

Melioidosis in Malay. A disease of rodents communicable to man. Resembles glanders and is usually fatal. *B. Whitmori* the causative organism.—A. T. Stanton and W. Fletcher, *Lancet*, i/1925, 1910.

Gonorrhœa. The *Micrococcus gonorrhœæ* is a medium-sized diplococcus; reniform in shape, occurring in groups, intracellular in character. This point is thought to be of no value in differential diagnosis, though previously stated to be so (see below). The organism is gram-negative.

Diagnosis of Gonococcal Infections

In the male, the gonococcus causes an acute urethritis in the first place. There is no difficulty in the recognition of this intracellular diplococcus in properly stained films made from the urethral discharge in the early stages of the infection. In the later stages of infection the gonococcus is not easily found and a more thorough examination is necessary. The following procedure is recommended in chronic cases and particularly when the patient seeks advice as to infectivity when contemplating matrimony. The patient should come for examination in the early morning with instructions not to pass urine till investigated. Films are made from any discharge in the urethra, and the urine passed and examined by naked eye for prostatic threads. The urine should be centrifuged and the deposit stained. The patient should then be placed in the knee-elbow position and the prostate

massaged. The prostatic fluid is collected and examined by film and cultures on serum agar. If a purulent morning discharge is absent, if there is no pus in the urine and if the prostatic fluid is clear and contains only mononuclear cells, the patient, in the absence of clinical signs and symptoms, is probably free from gonorrhœa.

The examination of the female genito-urinary tract for gonococcus is less commonly successful, even in the acute stage, and greater reliance should be placed on the cultural than on the film results.—Panton and Marrack.

Before pronouncing a woman free from infection at least three tests should be made. Films and cultures should be taken from the interior of the urethra, from the cervical canal after passing speculum, from the vagina, and if clinically infected, from Bartholin's duct.

The diplococcus can usually be readily found in large numbers in discharges of gonorrhœal origin, but a diplococcus of similar appearance is also apparently to be found not infrequently in vaginal discharge of non-gonococcal origin. If a distinction is to be made it is best to try to grow the organism in question on the ordinary forms of culture media, since, while the gonococcus will not grow on plain agar, it grows freely on blood agar. On the other hand, the other forms of diplococcus met with in the vagina usually grow freely on plain agar. It is also possible that the presence of the diplococcus inside the pus cell is characteristic of the gonococcus, but one must be a trained microscopist, who is continually examining such preparations, to be certain that what appears to be inside the cell is not really lying directly below or above it. Therefore, in cases in which a diagnosis is of serious importance, it should never be based on a mere clinical examination.—J. E. R. McDonagh.

Films made from discharge in a frank case of acute gonorrhœa are characteristic as regards the intracellular position of the gonococci but diagnosis can *not* be based on presence or absence of intracellular diplococci. For official purposes **Gram's method** of staining must be used.

In decolourising, *absolute* alcohol must be used, i.e. 98% or over. *Weak* alcohol decolorises gram-positive organisms. It should not be used for more than 2 minutes.—*Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 19, 1918; see also *Brit. med. J.*, ii/1918, 317.

The following is suggested to prevent error in Gram's method:

Take a small amount of debris from the gum tooth margin with a toothpick and spread near the right upper corner of the slide to cover a circular area of 0.5 cm. in diameter. Spread the material to be examined in the centre of the slide and treat the entire slide as if it contained one specimen. Place a drop of immersion oil over both smears and examine the test specimen in corner first; as this will always contain both gram-positive and gram-negative organisms there should be a sharp contrast between the blue-black of the former and the pinkish-red of the latter if the staining is satisfactory. One can thus state with assurance whether the organisms in the main specimen are gram-positive or gram-negative.—E. W. Hirsch, *J. Amer. med. Ass.*, ii/1928, 24.

W. Jensen, of Copenhagen, discards the use of aniline water, (2) increases the strength of the iodine solution, and (3) counterstains with neutral red.

After making the film in the ordinary way, fixing and cooling—

Stain with 0.5% aqueous methyl violet (6B) $\frac{1}{4}$ to $\frac{1}{2}$ minute. Pour off the bulk of the stain and wash away the remainder with a drop or two of *strong* Lugol's Solution (iodine 1, potassium iodide 2, water 100). Do not wash off with water. Pour on a fresh quantity of the Lugol and leave $\frac{1}{2}$ to 1 minute. Wash with *absolute* alcohol and pour on a fresh quantity of it moving the slide from side to side as in developing a photo plate. (A third washing may be necessary to complete decolorisation.) Finally, rinse with a few drops of alcohol and, without washing in water, stain with:

Neutral Red Solution. Neutral red 1 g., 1% acetic acid 2 ml., distilled water 1000 ml. (made stronger if necessary), for 15 seconds to 1 minute. Wash in water, dry and mount. The gonococci take up the red dye.

Pyronin Stain, *syn.* **Pappenheim's or Unna's Stain**, containing concentrated aqueous pyronin solution 1, concentrated methylgreen solution 3, is useful. Stain 5 minutes, wash and dry. Gonococci stain red; cells, etc., blue.

Wyatt Wingrave's Modification = Pyronin (water soluble) 2, methyl green 3, distilled water 100. Dissolve separately, mix and filter. After staining, wash with water and differentiate with 5% resorcin in alcohol.

All organisms, especially the gonococci, stain by this method a brilliant red and pus cells greenish-blue. The gonococci are found in regular clumps of diplococci, the distance between each pair being much the same. Some are intracellular.

Acid Thionin. Thionin 0.5%, glacial acetic acid 5% in distilled water. Stain 3 minutes, wash in tap water. A very reliable stain—shows phagocytosis well and the characteristic "kidney" shape of the cocci. Best stain for general use when confirmed by "Gram."—Wyatt Wingrave.

Nissl's Stain. Methylene blue, "B. Patent," 3.75, soft soap 1.75, water 1000. Stain thin smears (fixed in air) without heating, for 1 minute, wash, blot and examine.

Other Diplococci: *D. albicans amplius* Bumm, found in mucus in the healthy vagina; *D. albicans tardissimus*, morphologically identical with the gonococcus; *D. coryzæ*, *D. intracellularis meningitidis* (v. Cerebrospinal Fever), *D.* of orchitis (found in gonorrhœal pus during the first two days pathogenic), *D. pneumoniae*, *syn.* pneumococcus of Frankel, q.v., *D. pyogenes uræ*, and *D. catarrhalis*, vide *M. catarrhalis*.

N.B.—*Pneumococcus* is the only gram-positive diplococcus. Capsule well marked in pus, but not in culture. Cocci, elongated or lanceolate, converts oxy- into methæmoglobin in the culture. Will not grow on gelatin.

Cultivation

Comparative tests (under the Medical Research Committee) showed that (1) Thomson's Human Plasma-Glucose Agar, (2) Coles' Tryptic Blood Agar, (3) Gordon and Hine's Trypsinised Pea Extract Agar were satisfactory for cultivation. The last is for the meningococcus (*q.v.*) and if made of reaction +6 (Eyre's Scale) instead of +1 it would be improved for the gonococcus.

Human Plasma-Glucose Agar. To nutrient agar (2.5%) rendered +6 acid add sodium chloride 9 g., calcium chloride 0.25 g., potassium chloride 0.42 g. per litre and glucose 2.5%. The sterile tubed agar is melted in boiling water, and after cooling to about 50° add 1 ml. of human plasma to each tube and mix thoroughly by rolling the tube between the palms. For plating, the contents of three tubes may be added to a Petri dish.

To obtain human plasma. Draw off three-quarters of a test-tube full of blood with sterile precautions. Fill a sterile centrifuge tube, containing 2 ml. of 2% sodium citrate solution, with the freshly drawn blood. Plug with a sterile cork (keep the corks in alcohol and burn off the alcohol before plugging) and centrifuge. Pipette off the serum with a sterile 10 ml. pipette and add 1 ml. to each tube of agar as stated. (If the test-tube of blood is three-quarters full there is sufficient left for the Wassermann test.)

Using this medium the growth is profuse even in 18 hours.—D. Thomson, *Brit. med. J.*, i/1917, 869.

Isolation of gonococci may be effected from the fluid of gonococcic arthritic joints. It is not easy to obtain the gonococcus from the blood, although cultures are often obtained therefrom; when urethritis has ceased and fluids have

disappeared from the joints, one proceeds by drawing 2 ml. of the blood, with aseptic precaution, from the median basilic vein, mixing with double the quantity of agar and plating immediately.

Milk Broth or Milk Agar. Fresh milk 1000 ml. is mixed with 5 ml. of 1 in 4 hydrochloric acid and kept at 37° for 16 to 20 hours to precipitate casein, or the milk can be boiled, filtered and the filtrate neutralised with 10% sodium hydroxide—then place in autoclave 2 hours, boil, neutralise again and filter. The filtrate is mixed with equal parts of broth, or one or two parts of agar. Put into test tubes and sterilise.—J. E. R. McDonagh.

For **Cole and Onslow's Tryptic Broth** (and Agar), see p. 621.

For **Milk Serum (Sabouraud and Noire)**, see 18th Edn., p. 522.

Swartz's Medium made of veal and operating by cultivation in reduced oxygen tension, and **Hall's Testicular Infusion Agar**, are described by Stitt. **Complement Fixation**

As a result of a year's experience in using the test in women it is thought not sufficiently powerful to diagnose the disease; in the middle stages it will differentiate between gonococcal and non-gonococcal disease; and in the convalescent stage it is too delicate for use as a practical sign of cure.—J. J. Abraham, *Lancet*, i/1924, 431. *Further refs. Vol. II, 18th Edn., p. 524.*

Guinea Worm. *DRACUNCULUS MEDINENSIS*, *syn. D. Persarum, Filaria Dracunculus, F. Medinensis.*

Found in parts of India (Deccan, Scinde, etc.) in Tropical Africa, Persian Turkestan, Arabia, especially on West Coast of Africa. In parts of the latter nearly every negro has one or more specimens about him. The size of the female parasite is about $1\frac{1}{2}$ mm. by 90 cm. as average. Its habitat is the connective tissue of the limbs and trunk. It has been thought that the infection of man occurs by ingestion of infected cyclops, since 0.2% hydrochloric acid arouses the larvæ in an infected crustacean while the latter are killed. Evidence is fairly complete as to this mode of infection, but it must not be supposed that every species of cyclops can act as intermediary host. Leiper fed monkeys on bananas containing the infected cyclops and at the autopsy six months later obtained both male and female forms.

Epidemiology in Southern India studied by V. N. Moorthy (*Indian med. Gaz.*, 1932, 498 and 612). Adult worms develop in subcutaneous tissues some 9 months after swallowing well water containing the larvæ in cyclops or water fleas. In about 80% of infected cases the adult worms come to the surface of lower limbs and form blisters. Toxic symptoms such as urticaria, sickness and cyanosis, presumed to be of anaphylactic nature, are relieved by adrenaline chloride (1 : 1000) 5 to 7 m. subcutaneously.

Addition of copper sulphate 1 lb. to 200,000 gallons of water followed three days later by perchloron 3 lb. per 100,000 gallons suggested to be repeated after further 3 days and once a month during infective season from March to June. Straining infected water through cloth should not be neglected. Step wells should be replaced by tube wells or covered wells and pumps.

Hog Cholera. *B. suipestifer* (or *Bacillus ærtrycke*) has been isolated from cases of hog cholera, although the infection is now known to be due to a filterable virus. It has been found in the intestine of normal pigs, and may originate meat poisoning, especially where pork is the substance at fault. It shows close resemblance to *B. paratyphosus B* and to demonstrate it the method of absorption or complement fixation must be employed.

The true suipestifers fall into two sub-types. Sub-type 1, the American type, is almost exclusively confined to that continent and is the type isolated from American swine. It has serological differences and cultural distinctions, such as its failure to blacken lead acetate and inability to ferment dulcitol and arabinose.

Sub-type 2, the Western European type, isolated from swine in this country, is the one associated with *suipestifer* food-poisoning outbreaks. It regularly and rapidly blackens lead acetate and ferments both dulcitol and arabinose. This sub-type 2 can cause disease in man either in the form of food-poisoning or as illness of the type of paratyphoid fever.—*Lancet*, i/1933, 151.

B. suipestifer type mutton food poisoning.—W. Allen Young and G. D. Dawson, *Lancet*, ii/1922, 608. See also *ibid.*, 609.

Fatal case due to eating pork, infected by *B. suipestifer* *B.* The bacillus may also be found in mutton and beef. The disease varies in severity, fatal results being uncommon.—*Brit. med. J.*, ii/1924, 857.

See also *Food Poisoning*, under *Botulism*.

Influenza. Epidemic influenza in man caused primarily by a virus infection, and it is probable that in certain cases this infection facilitates invasion of the body by visible bacteria, giving rise to various complications. A disease was produced in ferrets by the intranasal instillation of filtrates of throat-washings from influenza patients—the disease is transmissible in ferrets, the infective agent only being recovered serially from the nasal passages of sick ferrets. Throat-washings from healthy persons and influenza convalescents caused no illness in ferrets, neither did the nasal secretions of a subject with a severe common cold. After recovery, the animals were immune to further attack. Human sera, especially from influenza convalescents, found to contain antibodies capable of neutralising the virus of the ferret disease. Swine influenza virus caused a disease in ferrets indistinguishable from that produced by human virus. Pig and human viruses have close antigenic relationships.—W. Smith, C. H. Andrewes and P. P. Laidlaw, *Lancet*, ii/1933, 66.

Periodicity of influenza. Evidence pointing to the existence in this country of a minor cycle of 33 weeks and in addition a major cycle round about 10 years maxima.—J. Brownlee, *Lancet*, ii/1919, 856; C. O. Stallybras, *Lancet*, i/1920, 372; see also B. E. Spear, *ibid.*, 589 and ii/1934, 1331.

Bacillus Influenzæ, *syn.* PFEIFFER'S BACILLUS. A very small bacillus, non-motile. Does not stain by Gram's method, nor grow on ordinary media unless hæmoglobin be present.

In mouths of all healthy individuals are to be found bacilli which cannot, by present methods, be distinguished from *B. influenzae*.—H. Fleming and I. H. Maclean, *Brit. J. exp. Path.*, 1930, 127.

The pneumococcus occurs very frequently in conjunction with the influenza bacillus. A mixed flora in the secretions in these cases is characteristic. Influenza bacilli are commonly found in the throat in pertussis, measles, and pulmonary tuberculosis.

Cultivation

B. influenzae grows best on a moist hæmoglobin agar containing no glucose—in many respects opposite to the gonococcus in cultivation requirements.—D. Thomson, *Lancet*, i/1919, 1106.

Blood Agar, made by boiling the agar medium with blood for a minute and separating the coagulated protein, is a good medium for growing *B. influenzae*. Or blood 1 ml. may be diluted with 9 ml. of water and boiled. The clear liquid added to nutrient agar is also an excellent medium for the organism, or strong mineral acids, e.g., sulphuric, may be used without heat to act upon blood, and the liquid subsequently neutralised with soda.—A. Fleming, *Lancet*, ii/1919, 138.

Blood digested by trypsin as medium for growing *B. influenzae*.—J. Matthews, *Lancet*, ii/1918, 104.

Paul Fildes' Medium. Mix in the following order N/1 saline solution 150 ml., hydrochloric acid 6 ml., defibrinated sheep's blood 50 ml., and pepsin B.P., 1 g. Shake to dissolve and place in water-bath at 55° for 2 to 3 days. Adjust the reaction to pH 7.6 by adding 20% sodium hydroxide solution 12 ml. or

more until a permanganate colour is produced with cresol red. Now add hydrochloric acid drop by drop until cresol red gives practically no change in colour but phenol red gives red (pH 7.0 to 7.2). Finally, add 0.25% chloroform. For use, add the medium directly to melted agar at 60° in a strength of 2% to 5% or to broth in the same proportion. It is not necessary to remove the chloroform. The correct adjustment of the reaction is important.

Distemper in Dogs. The Medical Research Council have studied the affection. There is good reason to think it offers a close parallel to human influenza.

The researches of Laidlaw and Dunkin at Mill Hill under the auspices of the *Field*, established a filter-passing virus as the primary ætiological factor and led to the introduction of methods of immunisation using a formalised preparation of the virus followed after an interval of some days by the untreated virus. The *B. bronchisepticus*, formerly held by some to be the primary causative organism is probably only of secondary importance, although it has been stated that dogs immunised to the virus can be infected with *B. bronchisepticus* and develop symptoms indistinguishable from virus distemper. (See *Vet. J.*, 1931, 548 and 1933, 1; also *Vet. Rec.*, 1931, 371; 1934, 376, 1495; and 1935, 464, 802.)

There are three varieties of distemper—head, chest, and abdominal—the head being the most serious, as in this the virus has attacked the central nervous system and it is likely to lead to chorea. Sudden and unexpected nervous or paralytic seizures are seen. Infection may possibly depend on nutrition and conditions of the dog. Diet, and small frequent doses of quinine salicylate are advised.—*Chem. & Drugg.*, ii/1926, 462.

Leishmaniasis

Leishmania parasites give rise to several diseases, including kala-azar and oriental sore:

Kala-Azar. Occurs in India, China, S. Russia, Mesopotamia, the Mediterranean littoral, the Blue Nile, and in Kenya Colony and is a disease of children or young adults. Left untreated, nearly always ends fatally in a few months in acute cases, or in a few years in chronic cases. There seems no reason to separate the Mediterranean leishmania from that of India, and the parasite of kala-azar wherever it occurs may be designated *L. donovani*. Diagnosis is established by discovery of its parasite, by making films of material obtained by puncture of the spleen (or of the liver, which is less dangerous) and staining by Romanowsky stain. It is generally assumed that *L. donovani* has an invertebrate host, e.g., bugs or fleas, but the problem still remains unsolved.

Oriental Sore, *syn.* Tropical Ulcer, Delhi Boil, also (in the New World) Espundia, Uta, Buba, Pian-bois, Forest Yaws and Bosch Yaws.

Oriental sore is widely distributed: it occurs in Spain, Italy, Greece, N. Africa, Egypt and the Sudan, Asia Minor, Arabia, Mesopotamia, Persia, S. Russia, India and S. America. The disease in the New World seems to be more severe and of longer duration than in the Old World, and the parasites causing the two diseases may not be identical, but it seems better to retain the name *L. tropica* for both forms until more reliable proof of difference is forthcoming.—Wenyon.

In addition to “*espundia*,” in Brazil, there is a further leishmania infection introduced from the Eastern Mediterranean known as “Aleppo bouton,” a systemic disease.—H. R. Carter *Int. Conf. Trop. Amer.*, 1924, 483.

The oval "**Leishman-Donovan**" bodies ($2.5 \times 3 \mu$) are present in every case of kala-azar, and are the cause of this deadly disease. Sir L. Rogers in 1904 found that if kept in a sodium citrate solution at about 22° these bodies undergo multiplication, showing that they are capable of living outside the human body in some cold-blooded animal, possibly an insect, but the life history remains to be completed. Similar parasites have been found in oriental sore and more recently in a variety of other ulcerative affections in tropical America and in the Sudan, one of them—*espundia*—being a very grave disease.—Sir Patrick Manson, *Brit. med. J.*, ii/1917, 105.

Noguchi has shown that the leishmanias found in dermal conditions are different from the leishmania of kala-azar, and the old theory that oriental sore is merely a manifestation of kala-azar is entirely disproved.—A. Castellani, *Int. Conf. Trop. Amer.*, 1924, 479.

Cultivation. *Leishmania donovani*, *L. infantum*, *L. tropica* and *L. brasiliensis* grow well on semi-fluid agar medium and form heavy greyish surface growth several millimetres in depth. All the strains require oxygen for growth and none grow in atmosphere of hydrogen, nitrogen, or carbon dioxide. Distilled water caused immediate disintegration of flagellates, while tonicity from 0.3% to 0.9% sodium chloride is well borne. Organisms immobilised by half saturated saline solution. Saponin in 1 : 10,000 dilution killed cultures without dissolution of bodies or flagella. Ricin 1 : 1000 caused immobilisation and agglutination. *L. donovani*, *L. tropica* and *L. brasiliensis* each represent a serologically independent and distinct unit. *L. infantum* serologically identical with, or closely allied to, *L. donovani*. These findings conform with clinical observations which indicate that visceral leishmaniasis (*L. donovani* and *L. infantum*) are distinct from benign oriental sore (*L. tropica*) and probably also from the American type of leishmaniasis (*L. brasiliensis*).—H. Noguchi, *Int. Conf. Trop. Amer.*, 1924, 466.

Formula for culture medium (plate method) used for cultivation of *Leishmania* parasites: Agar 30 g.; dextrose 20 g.; slightly alkaline Liebig's broth 1000 ml.—J. C. Ray, *Indian J. med. Res.*, 1932, 355.

Aetiology. The ætiology of kala-azar and tropical sore.—B. Blacklock, *Lancet*, ii/1923, 273.

The life-cycle of kala-azar.—*Lancet*, ii/1926, 506.

Transmission. The bed-bug and the common louse exonerated from transmission of kala-azar. "For the present, the sand-fly (*Phlebotomus argentipes*) must be held to be the probable transmitter." The parasite of kala-azar should be known as *Herpetomonas donovani*. Report of Kala-azar Commission in India.—*Lancet*, ii/1926, 140.

Infantile or Mediterranean form of kala-azar common in some districts of south of France. Dogs considered a frequent, but not invariable source of infection; ticks convey infection from one dog to another and possibly also to children.—P. Giraud, *Pr. méd.*, 1932, 1368.

While the remarkable development of the parasite in the sand-fly throws grave suspicion on this insect, the failure to procure infection readily by its bite should indicate that other methods of infection still have to be considered.—Second Report (1926-1930) of Kala-azar Commission, India, per *Brit. med. J.*, ii/1932, 890.

Infection may occur from earliest skin lesions; incompletely cured cases of kala-azar develop numerous nodules in the skin containing *L. donovani* and are a possible source of infection. *Phlebotomus argentipides* infected experimentally from these lesions.—L. E. Napier, R. O. A. Smith and C. R. Das Gupta, *Indian J. med. Res.*, 1933, 173.

Diagnosis. *Test for kala-azar.* Add 2 ml. of patient's blood, taken from one of the ante-cubital veins, to a solution of 0.1 g. urea-stibamine in 3 ml. distilled water. In positive cases a thick, white, curdy precipitate appears

almost instantly.—*Indian med. Gaz.*, Dec. 1927, per *J. trop. Med. (Hyg.)* 1928, 87.

In a well-established case, the serum sets immediately, like the white of an egg. There is marked leucopenia and a great reduction in proportion of white to red corpuscles. By careful examination of blood films, the parasite can be found in the peripheral blood in nearly 100% of cases.—Napier and Muir, *Brit. med. J.*, ii/1923, 719-720.

Spleen puncture will show evidence of large numbers of typical parasites. Diagnostic—diarrhœa and splenomegaly. The latter is not so marked in enteric as in kala-azar and is not so solid to the feel.—G. R. Ward, *Lancet* ii/1916, 16.

The treatment of kala-azar is dealt with in Vol. I, p. 160.

Treatment of oriental sore. Oriental sore must no longer be regarded as a local disease, and a vaccine from *L. tropica* has been used with encouraging results. Berberine sulphate should never be given where there is sepsis or inflammation. Sores may be classified into two types—and 1% and 2% solutions of berberine should be used respectively. The maximum amount of solution which may be injected is 4 ml. of a 1% solution and it is not considered necessary to give a local anæsthetic prior to infiltration. Intravenous injections of tartar emetic solution have so far given better results than have any other organo-antimony preparations.—Warma, *Indian med. Gaz.*, Nov., 1934.

The morbidity rate from this disease is enormous and if left untreated death ensues in nearly every case. There is good reason to suppose that in its mortality and morbidity tropical ulcer may take its place with malaria, plague and trypanosomiasis. Nearly every variety of organism has been blamed for producing the condition but in no case has the evidence adduced been convincing. The fact that spirochætes and fusiform bacilli, for instance, are found constantly in these lesions is of no scientific value ætiologically, as it is the exception for such organisms to be absent from any wound of skin or mucous membrane in tropical countries. On the other hand, there are strong grounds for viewing it as a deficiency disease (calcium deficiency) and it is significant that it is found always amongst the poorest classes, and never among chiefs or their families. On this assumption calcium chloride injections have been given (15 grains in 10 ml. distilled water daily intravenously) in some 500 cases with remarkable results. Without exception every trace of offensive odour disappears in 3 or 4 days and within 10 days the ulcer is clean.—L. J. A. Loewenthal (Uganda), *Lancet* ii/1932, 889. See also G. A. Stephens, *ibid.*, 1026.

A satisfactory and surprisingly successful method has been found in excision and skin graft, seeds being the surest and easiest of application, combined in suitable cases with Thiersch grafts. Average time for complete epithelialisation of the area 13 days.—C. James, *ibid.*, 1095.

A bibliography of recent investigations on tropical ulcer carried out in Kenya Colony.—J. H. Sequeira, *Lancet*, i/1933, 57.

Immunity to oriental sore. The natives of the Turkestan and the Caucasus develop a natural immunity, and new arrivals to the district are always more apt to become infected than the settlers. Complete immunity can be brought about by an experimental sore, but only when it is allowed to develop and heal naturally. Preventive inoculation on covered parts of the body can be recommended, if care is taken to avoid sepsis or inoculation of syphilis.—E. I. Mazinowsky and A. Schurenkova, *Trans. R. Soc. trop. Med. Hyg.*, 1924, 67.

Leprosy. *Bacillus lepræ* (Hansen's bacillus) has a morphology similar to *B. tuberculosis*, but usually occurs more in clumps and is said to be tapered at the ends. It stains irregularly, and is more readily decolorised than *B. tuberculosis* by inorganic acids.

Obtain material from a nodule, and stain the smear by Ziehl-Neelsen, using 20% sulphuric acid, or by Gram, counterstaining with bismarck brown. The organisms are gram-positive. Finding *B. lepræ* in nodules is usually easy, but it is extremely difficult to find in the spots of nerve leprosy; the nasal mucus should be examined, after giving a large dose (60 grains) of potassium

iodide. The following features distinguish them from tubercle bacilli; they occur grouped together in huge numbers, stain more solidly, and granules when present are coarser and are decolorised more easily. Certain cultivation or inoculation into experimental animals with pathogenic results is not possible.—Stitt.

"Victoria Blue," as a stain for *B. lepræ* (Mühlpfordt), has a definite affinity for lipoids and hence for spirochætes. Schümacher's modification is: Victoria blue (2 parts) dissolved in 50% alcohol, mixed with equal quantity of 4% solution of phenol, to which is added 10% aqueous solution of glycerin. The smear containing spirochætes is fixed with alcohol, the solution poured over the slide and heated for 15 seconds.—*Brit. med. J. Epit.*, i/1925, 14.

Cultivation. The most favourable medium for growth appears to be either placental-extract-agar or horse serum nutrose-agar with the addition of 2% ground-up smegma bacilli. Kedrowsky's work on the variable morphology and staining properties of the lepra bacillus is confirmed. Agglutination, precipitation, complement-deviation and percutaneous tests can be used to prove the relationship of acid-fast or other germs cultured from cases of leprosy. Rat and human leprosy appear to be identical diseases. It is therefore possible that the germ of both can be transmitted from one to the other, given an appropriate intermediary.—Bayon, *Brit. med. J.*, ii/1911, 1269; *Lancet*, ii/1911, 460. See also C. Duval, *Brit. med. J.*, ii/1912, 1189; M. E. Marchoux, *ibid.*, 1191; also *Lancet*, ii/1912, 1791, and W. J. Kedrowsky, *J. Trop. Med. (Hyg.)*, 1928, 21, and 1922, 216.

Hansen's bacillus can be grown readily by planting out in a medium made from minced chick embryo suspended in Tyrode solution; growth obtained in 5 days under atmospheric conditions and also under oxygen and CO₂ tension; bacillus remained viable for 2 years.—E. B. McKinley and E. Verder, *Proc. Soc. exp. Biol.*, N.Y., 1933, Feb., 659.

Incubation Period. An analysis of 84 cases recorded shows that the disease developed in within less than 5 years after exposure to infection in 92% of them. The average period between exposure to infection and the development of the disease was 2 years and 2 months. There is a direct relationship between the closeness of contact with the disease and the early development of symptoms, the incubation period of a few cases of direct inoculation being under 2 years and usually about 6 months.—Sir L. Rogers, *Indian med. Gaz.*, Feb. 1924, per *J. trop. Med. (Hyg.)*, 1924, 72.

Transmission. The presence of *B. lepræ* in the mosquito (*Culex pungens*) and in the bed bug (*Cimex lectularia*) has been shown.

The view that the spread of leprosy in S. America has a definite relation to the bugs and mosquitoes was discussed in the 19th Edn., Vol. II. So far as Brazil is concerned the former could not be blamed, because for some unexplained reason bed-bugs do not exist in the Amazonian villages.

Some interesting experiments showed that flies, mosquitoes and other insects spread it, but in particular *Acanthia lectularia* appears to constitute a very important agent in the spread. Acid-fast bacilli resembling *B. lepræ* have been found in 30% of specimens up to 16 days after feeding on lepers.—T. Lindsay Sandes, *Brit. med. J.*, ii/1911, 469.

15% of general skin out-patients in the Skin Diseases Clinic of the Calcutta School of Tropical Medicine are early and undiagnosed cases of leprosy. Evidence points to inoculation as method of transmission. Those living in contact with infectious cases get lepra bacilli on their skins, a scratch or lesion implanting the bacilli under the skin; there is always, if looked for, a herald lesion. The mutilated, anæsthetic cases are not infectious but the early, nodular cases, unsuspected, and undiagnosed, are. They should be segregated in preference.—*Indian med. Gaz.*, 1924, 354.

In a case of leprosy at the Pasteur Hospital there were numerous scars resulting from the slow healing of ulcers, and when their surface, or the nasal mucous membrane, was slightly scraped and the substance obtained examined under the microscope, numerous fine, short, cocciform bacilli were seen, to which Prof. Manchoux provisionally gave the name *Mycobacterium pulviforme*. After death, great quantities of these were found in the skin, lymph glands, liver and spleen. As a result of inoculation from this spleen, 5 out of 7 rats contracted a disease practically identical with rat leprosy. The relation of rat leprosy to human

leprosy may be similar to that of bovine to human tuberculosis. 0·6% of Parisian sewer rats are definitely leprosy.—*Lancet*, ii/1923, 1309.

HEREDITARY TRANSMISSION of predisposition difficult to prove. Of 398 children of leprosy parents, 231 were non-leprosy and no case of congenital leprosy was observed.—per *Prescriber*, 1928, 211.

Distribution. Equatorial Africa has a higher incidence of leprosy than any other region in the world, the rate being as high as 130 per 1000 in the Ebolawa District. The total number of lepers in China is estimated at 1,000,000 in 1912 Japan had 102,000 lepers, and in 1921 India had about the same number. Chinese immigrants seem to have been an important factor in the spread of leprosy. Every country with a high leprosy incidence is within the tropics, and practically all of them have a high rainfall, the disease being nearly or completely absent from those parts in which the rainfall is less than 10 inches.—A review of "Leprosy" (Rogers and Muir), *J. Amer. med. Ass.*, ii/1925, 381.

According to census figures there are 102,000 lepers in India, but these are only the advanced cases, and for every advanced case there are about five earlier cases.—E. Muir, *Trans. R. Soc. trop. Med. Hyg.*, Aug. 1931, 96.

HIGH RAINFALL and humidity increase the incidence in large areas in India and poverty of diet and consumption of decomposed fish are predisposing factors.—per *Prescriber*, 1928, 211.

Contact cases of leprosy in the British Isles.—J. M. H. MacLeod, *Brit. med. J.*, i/1925, 107.

IN CHINA leprosy seems to be specially associated with water-logged and ill-drained areas. But for the aid rendered by the Christian Church the lot of the leper in China to-day would be hopeless. Modern scientific methods, coupled with a voluntary form of segregation on the part of the lepers themselves, give good prospects of changing the entire outlook of China's lepers, and ultimately of ridding China of leprosy.—*China med. J.*, per *J. Amer. med. Ass.* ii/1925, 1931.

Diagnosis. *Histamine test as an aid in the diagnosis of early leprosy.* When a dilute solution of histamine is pricked into the normal skin a sharply defined circular local reddening appears in about 20 seconds, followed in another 15 to 30 seconds by a flush or *flare* of a dark red or scarlet colour on the surrounding skin, and later by a discreet wheal at the site of the prick. For the diagnostic test of early leprosy a 1:1000 dilution of histamine phosphate in normal saline solution is employed. A small drop of the solution is carefully placed within the suspicious macule to be tested and another dropped on normal skin at least one inch away from the border of the lesion for control. With a sharp pin-prick is made through the drop into the skin underneath, taking care to avoid bleeding. The histamine solution is wiped off immediately and the pricks closely observed, under good, natural light. The test is said to be negative when the complete response is elicited and positive when the flare is absent. The flush is always absent in the depigmented macule of leprosy; the wheal in the macule is usually the same size as that on the normal skin. The test has been applied on macules of other skin diseases which may be mistaken for the pale macule of leprosy, but in every case the flare is present provided the individual is not unsusceptible to histamine. In the case of the reddish macule of leprosy only the wheal may be elicited, but when the colour is not so striking the local redness may be seen. When the redness of the original lesion is at all bright it is best to prick the histamine solution just inside the border; in the non-leprotic lesion the flare appears on the adjacent portion of the skin outside the border, whereas there is no such flare extending from the macule in early leprosy.—J. Rodriguez and F. C. Plantilla, *Leprosy Rev.*, 1932, 18.

Investigation of certain serological reactions in leprosy.—E. Slack, *Leprosy Rev.*, 1932, 28.

Treatment. Leprosy essentially a disease of the unhealthy—little chance of arresting disease unless predisposing causes, e.g., syphilis, malaria, etc., are dealt with. It is now an established fact that **only about 3% of lepers actually die of leprosy**. Many lepers cannot be helped much because the anæsthesia and other signs of nerve lesions are often result of nerve destruction, the leprosy having died out.—R. G. Cochrane, *Lancet*, ii/1926, 95.

The important advance made in the treatment of leprosy in India is the adoption of potassium iodide. Clinical and pathological study at the Calcutta

School has led to classification of certain types and phases of leprosy which benefit from iodide. (Report of the Indian Council of the B.E. Leprosy Relief Assn.).—*Lancet*, ii/1928, 472.

A thorough disinfection of the nose is one of the first essentials in treatment. A solution of ammonium persulphate 3·7% and hydrochloric acid 1% in water has been used. Inhalation of the fumes of **burning sulphur** has also been employed.

Various dyes given intravenously: diminution of external lesions after following:—25 ml. 4% trypan blue; 10 to 20 ml. of 1% brilliant green; 10 ml. of 2% fluorescein—too early to say if improvement permanent. Trypan blue and fluorescein together produce marked retrogression of lesions in about 9 weeks.—G. A. Ryrie, *Trans. R. Soc. trop. Med. Hyg.*, June 22, 1933, 33.

Leprosy: a self-healing disease. The natural and *increased production of lipase*, or fat-splitting ferment in the blood and tissues is an important factor in the protective processes or induced resistance of the body, which offers a reasonable explanation of the therapeutic effect of sodium morrhuate and, in part, of sodium chaulmoograte, both of which increase the action of lipase *in vitro*.—J. A. Shaw-Mackenzie, *Lancet*, i/1924, 518. The *blood lipase* in turn dissolves the fatty coating of the leprosy bacillus (and the tubercle bacillus) Sir L. Rogers, *Brit. med. J.*, ii/1923, 11.

The normal course of leprosy is that of a self-healing disease, like smallpox, enteric and other diseases, but whilst enteric completes its course in, say, 21 days, leprosy may take 21 years to burn itself out. Most of the treatments of leprosy which have had any vogue owe a great part of their successes to the fact that leprosy tends to get better spontaneously and hopeful suggestion helps the tendency to cure. It is criminal to assert that leprosy is not amenable to treatment, though perhaps equally wrong to claim that there is a specific cure. Leprosy is a disease which can be benefited by treatment, the majority of early cases having a fair chance of losing all signs for the rest of their lives, providing their general health is maintained. The infectiousness is exaggerated. In any country in which the incidence of the disease remains the same over a long period of years, each victim, on the average, communicates the disease to one other person.—Leader, *Indian med. Gaz.*, June 1924, 299.

Predisposing causes.—E. Muir, *Lancet*, i/1925, 169.

The Chaulmoogra Treatment is in Vol. I, p. 602: Leprosy as a self-healing disease, ibid., p. 608: Vaccine Treatment, ibid., p. 609: see also Therapeutic Index, ibid., p. 1065.

Malaria

Classification of the Malarial Parasites. That adopted by Manson in his "Tropical Medicine" and generally accepted may here be briefly cited.

The forms of the parasite and of the diseases to which they give rise are divisible into two groups—the benign and malignant.

The benign parasites never form crescent bodies, whilst the malignant, or at least the most important of them—the subtertian, do; i.e. the gamete of the benign parasite is a sphere or disc, that of the malignant parasite a crescent.

Clinically, the benign parasites rarely give rise to pernicious attacks, while the malignant frequently do.

(i) **Benign parasites** are of two kinds: **Quartan** parasites with cycle of 72 hours, causing fever recurring every 3 days—"Quartan Fever"; the other, the **Tertian** parasite with cycle of 48 hours, causing fever every 2 days—"Tertian Fever." (In deeply stained preparations of the tertian parasite the hæmoglobin of the red blood corpuscles in question will be dotted over with granules known as *Schuffner's Dots*—a feature of some diagnostic value.)

(ii) **Malignant parasites:** a pigmented parasite; the *Subtertian* (syn. *Æstivo-Autumnal* of the Italians or *Tropical* of Koch) of 48, or approximately 48, hours' cycle.

Staining. Films of blood smeared evenly with a very small quantity, dried in the air, not by aid of a flame, and fixed by immersing in alcohol and ether in equal parts, 10 minutes, may be stained with aqueous methylene blue and eosin or with methylene blue alone, 5 minutes, or with a hæmatoxylin stain, or by Leishman's stain (*q.v.*). With Leishman's stain fixing is not necessary. Muir says the structure of the parasites is well brought out by the following—Soak film in saturated corrosive sublimate solution a few seconds. Wash well, stain with hæmalum 10 minutes, wash, stain again for about the same time with aqueous methylene blue. Wash in water, dehydrate, clear in xylol and mount in balsam. The chromatin of the parasites is violet blue, and the protoplasm purplish blue. The Leishman method is, however, principally in use. Consult Allbutt's *System of Medicine*, or Muir and Ritchie.

Leishman's stain made by dissolving 1 g. of the powder in 200 ml. of methyl alcohol and 12 drops of 1% NaOH added. Used for general purposes. In staining, stain for 30 seconds with this, then dilute with distilled water about 1 in 4 for a further 2 to 3 minutes. Wash with distilled water and drain. Gauducheau's stain used when Leishman's fails.—P. Manson-Bahr, *Lancet*, i/1920, 79.

Gauducheau's stain has the following composition:—

Borrel's blue	6 ml.
1% Methylene blue in 90% alcohol	18 ml.
0.5% Water-soluble eosin (blue shade) in dehydrated alcohol	30 ml.
Dehydrated alcohol	140 ml.

In use, apply the stain, undiluted, to the film, leaving it on about one minute. Then dilute with four parts of distilled water (*neutral*). Each batch of stain requires a different length of time for standing. New stain requires about half an hour, old stain about 20 minutes. In the East, 20 minutes for new stain and 7 minutes for old stain were found sufficient, but in England it takes longer.

Borrel's Blue may be made as follows:—

Dissolve a small handful of silver nitrate crystals in hot distilled water in 100 ml. flask. Fill up with 10% caustic potash solution. Wash the resulting precipitate of silver oxide about 12 times in boiling distilled water, then fill up the flask with saturated aqueous solution of medicinal methylene blue. Plug the flask loosely with cotton wool and place in direct sunlight for a day or two (this prevents subsequent precipitation when the stain is exposed to light during later use). Then cork, place in the incubator at 37° for one month, removing cork and shaking occasionally. Filter at end of month; the filtrate = Borrel's blue. Details kindly supplied by J. Graham Willmore.

Some modifications in the thick-film method in the examination of blood from malaria parasites.—M. A. Barber and W. H. W. Komp, *Int. Conf. Trop. Amer.*, 1924, 110.

Thick blood films dried some hours, stained within 24 hours with Giemsa stain in buffered water containing 1 g. KH_2PO_4 and 2 g. Na_2HPO_4 to pH 7.—R. Green, *Trans. R. Soc. trop. Med. Hyg.*, Nov. 1, 1932.

Manson's Method for Demonstrating Flagellate Bodies in Malaria. Blood films are dried and fixed in absolute alcohol (5 minutes). Hæmoglobin is washed out by dropping on 15% acetic acid. The film is then washed in water and stained for 6 hours or longer in 20% carbol fuchsine. It is then washed, dried, and mounted as usual.—“Essentials of Practical Bacteriology,” H. Curtis.

Cultivation of the malarial parasite in vitro. 51 cases.—L. S. Dudgeon and C. Clarke, *Lancet*, i/1917, 530.

Ætiology. There exist sexual (sporogony in the mosquito) and non-sexual (schizogony in man) cycles of the parasite. Various workers, notably Grass and others, have observed the complete development of the malignant parasite in *Anopheles Claviger* and the partial development of the tertian parasite in the same anopheline. (For a historical account see Wenyon, Vol. II, p. 909.)

Histology. Histology of cases rapidly fatal in the Salonica force in 1916. Examinations of brain, heart, muscle, adrenal glands, kidney, liver, etc.—L. S. Dudgeon and C. Clarke, *Lancet*, ii/1917, 153.

Malaria, 12,000 cases in Macedonia, treated by A. C. Alport (Review).—*Brit. med. J.*, ii/1919, 467. Thyroid gland enlargement in malaria.—J. B. Hume, *Brit. med. J.*, ii/1919, 661.

Localisation of malarial parasites in man.—W. M. James, *Int. Conf. Trop. Amer.*, 1924, 67.

EGYPTIAN EXPEDITIONARY FORCE, malaria in, during $3\frac{1}{2}$ years. Epidemiology, microscopy, etc., concerning (1) Egypt and the Canal Zone, and (2) Palestine. Caused by two species of parasite—the benign tertian and the malignant or subtertian. The quartan appears to be almost non-existent in Egypt and to occur rarely in Palestine.

Transmission. The mosquito malaria theory was formulated by Sir P. Manson in 1894. From the fact that the flagellate body does not come into existence until the blood has left the blood vessels—that is until it is outside the body—he concluded that the function of the flagellum lay outside the body—in fact that the flagellate body was the first phase of the extracorporeal life. As the parasite while in the circulation is always enclosed in a blood corpuscle and therefore unable to leave the body by its own efforts, its removal must be effected by some blood sucker. The mosquito was correctly suspected. Sir Ronald Ross proved finally in 1898 the extracorporeal phase of the parasite.

Mosquito-malaria theory. A good summary of the proof of the theory, commencing with the discovery of the parasite by Laveran in 1880.—Sir Patrick Manson, *Brit. med. J.*, ii/1917, 103. See also R. McCarrison, *ibid.*, 109.

It has been computed that $\frac{1}{4}$ billion parasites must be present to produce fever, but in an experimental "inoculation" not one parasite could be found in the blood during the first three days of fever, while during the last three days, as the fever subsided, parasites were found.—M. D. O'Connell, *Lancet*, i/1920, 518.

KEY TO ANOPHELINE SPECIES OF INDIA, CEYLON, AND MALAYA. Of benefit to the tropical practitioner. An outstanding example of simplicity, conciseness and accuracy—19 pp. by Prof. Strickland.—Review *Brit. med. J.*, ii/1925, 851.

Classification of American anopheline mosquitoes and their relation to the transmission of malaria.—F. M. Root, *Inf. Conf. Trop. Amer.*, 1924, 148-156.

The main mosquito intermediary in the benign tertian zone in Palestine appears to be the spot wing (*A. maculipennis*) and in the Jordan Valley *A. Palestinensis*.—P. Manson-Bahr, *Lancet*, i/1920, 79.

Man is the only malaria-carrier. Any person infected with malaria, irrespective of number of parasites present, may become an effective carrier and a source of infection. The malaria-carrier bears a direct relation to malaria prevalence.—C. C. Bass, *Int. Conf. Trop. Amer.*, 1924, 61.

Malaria Control. To prevent the spread of malaria it is customary to improve surface drainage and so obviate breeding places of the larvæ of the mosquito. Wire gauze, netting, etc., are employed as protectives to man.

Antilarval Measures. Common kerosene poured on the surface of pools, lakes, etc., is useful. It forms a scum which prevents the larvæ from breathing and hence kills them. See also First Internat. Congress, *Brit. med. J.*, ii/1925, 970.

Thirty pounds of oil will cover at least 2000 square yards of water; the dose of paraffin should be repeated about 20 times during the year.

"Bamber Oil." Citronella oil (not lemon grass oil) $1\frac{1}{2}$, kerosene (paraffin) oil 1, coconut oil 2, to which is added 1% of phenol. As a preventive against malaria instead of the mosquito net. Its efficacy lasts 4 to 6 hours—sufficient for a night's sleep when a net is not available.—C. Christy, *Lancet*, ii/1917, 482.

Rice cultivation with the necessary stagnant water is no small source of increase of malarial disease.

Irrigation of rice fields around the coolie lines in North Bengal should be abandoned as malaria here is man-made through erroneous clearing of jungle along streams.—C. C. Hamson and G. C. Ramsey, *J. trop. Med. (Hyg.)*, 1933, 33; see also H. G. Winter, *J. R. Army med. Cps*, 1934, 238.

Paraform recommended for destruction of anopheline larvæ, 0.25 g. (mixed with chalk 0.08 g. in calm weather, or sand 20 g. in windy weather) is used for each square metre of surface.—Roubaud, *Trop. Dis. Bull.*, 1921, 115.

Smoke production as a measure of mosquito control.—J. M. Shapiro, per *J. trop. Med. (Hyg.)*, 1923, 46.

The use of gases and vapours for killing mosquitoes breeding in wells.—K. B. Williamson, *Trans. R. Soc. trop. Med. Hyg.*, 1924, 485.

A few drops of **carbon disulphide** poured into a 10-gallon tub, the water of which was swarming with the larvæ of mosquitoes, killed them all in half an hour, without affecting the water either in taste or smell.—A. K. Fisher, *J. trop. Med. (Hyg.)*, 1923, 340.

Excellent résumé of advice for soldiers and others on prevention of malaria.—C. Christy, *Lancet*, ii/1917, 485.

The cost of malaria control.—J. A. Le Prince, *Int. Conf. Trop. Amer.*, 1924, 157-164.

Larvicides in mosquito control, using White Cross cresylic disinfectant.—J. F. Marshall, *Lancet*, i/1925, 1380.

Some aspects of malaria control.—W. E. Deeks, *J. trop. Med. (Hyg.)*, 1926, 185-194.

Subtle chemical differences (alkalinity or acidity) in breeding waters may be a factor in determining species of larvæ found in them.—*Rep. Int. med. Res. F.M.S.*, per *Brit. med. J.*, i/1926, 1053.

Diagnosis of Latent Malaria. Technique of new test: A set of 9 dilutions of patients' serum is prepared ranging from 1:2 to 1:512 in distilled water and to each is added an equal volume (0.4 ml.) of a melanin pigment solution and the series incubated at 37° for 5½ hours. The melanin pigment solution is derived from human hair by hydrolysis with 50% HCl, followed by concentration *in vacuo* and purification by dialysis. Positive results are observed as white granular precipitates forming at the foot of the tube; the degree of positivity is determined by noting the highest dilution of the patients' serum showing precipitation. The rise and fall of the reacting principle in human malarial serum with melanin pigment may thus be quantitatively ascertained during an attack. Reaction shows about the fifth to seventh day after infection, although no parasites may be seen at this stage. The maximum titre of 1:128 is reached about the fourth week and then rapidly declines. The authors suggest that the term melanoflocculation test be altered to melano-precipitation reaction.—Greig, Rooyen and Hendry, *Lancet*, i/1934, 1393.

Adrenalin subcutaneously, 0.5 to 1 ml. of a 1 in 1000 solution, causes plasmodia to appear in the blood in 15 to 60 minutes.—Per *Prescriber*, 1928, 372.

A TEST FOR THE DIFFERENTIATION OF MALARIA FROM KALA-AZAR, ENTERIC, ETC. Draw four parts of blood into a syringe containing one part of 5% sodium citrate solution. Pour to the 24 mm. mark in a 60 mm. graduated tube, and allow to stand. In healthy men, sedimentation is slow, the column of corpuscles never being less than 23 mm. after half an hour, and the supernatant fluid cloudy or faint yellow. In kala-azar sedimentation is rapid—under 10 mm.—and the fluid clear and colourless or faintly greenish. In typhoid the column is 13 mm. to 15 mm., and the fluid cloudy white. In malaria it varies between 5 mm. and 22 mm., with an average of 12 where plasmodia are found, and the fluid is markedly yellow.—*Indian J. med. Res.*, Jan. 1927, per *Prescriber*, Nov. 1928, 372.

For treatment and prophylaxis of malaria see Vol I.

Malta Fever. See UNDULANT FEVER.

Measles. The ætiology of measles is still unknown, but it is thought to be due to a filter-passing virus.

Seroprophylaxis. Methods of using serum to achieve passive immunity:

- (1) Injection into healthy contacts; immunity lasts a month.
- (2) Injection during first 5 or 6 days of incubation period; patient will not develop measles.

(3) Injection after 6th and before 9th day; modifies attack.

(4) Injection at beginning of period of invasion (10th day) results only in *local* inhibition of rash.

Results decidedly favourable. Municipal collecting and distributing centres for serum established in Germany, France and America.

To produce active immunity, inject 10 ml. convalescent serum and 24 hours later 1 ml. of blood from an early case. If injection of blood is repeated, immunity may be permanent.—S. M. Copeman, *Brit. med. J.*, i/1928, 835.

Convalescent Serum. Gave protection in over 95% of cases. Dose from 3 ml. under one year, increasing by 1 ml. up to 7 ml. for those over 5 years; 10 ml. at 10 to 12, and 12 ml. for adults. No ill-effects, but not advised in infants under 6 months. For complete protection, serum must be given before fifth day of incubation, with modified protection up to ninth day. Of no value after ninth day.—D. Nabarro, *Lancet*, ii/1932, 573.

Injections of 5 ml., even up to eight or tenth day of exposure, of great benefit. Complete protection secured in 185 out of 233 patients (80%), whereas 23 out of 32 controls contracted measles.—T. M. Hunter, *Brit. med. J.*, i/1933, 218.

Adult serum. The blood of normal adults is a valuable source of antitoxin. While 23 infants left unprotected during an epidemic all suffered from a typical attack, 13 out of 56 injected with 30 ml. of parental blood escaped entirely and the remainder only had a mild attack.—J. M. Lewis and L. H. Barenberg, *N.Y. St. J. Med.*, Jan. 15, 1932, per *Brit. med. J.*, i/1933, 423.

In the epidemic of 1931-32, during which 11,526 cases were admitted to the L.C.C. Hospitals, comparisons were made of the results obtained with convalescent and adult serums, with the conclusion that 90% prevention was secured by convalescent and nearly 80% by adult serum, and that adult serum used in prevention yielded about 70% better results than those in untreated or control cases. "Adult serum a valuable therapeutic agent which can be used in the treatment of measles on a larger scale than is possible with human convalescent serum."—Rept. of M.O.H. and School M.O. on the Measles Epidemic, 1931-32, *Brit. med. J.*, ii/1933, 830.

Measles is unavoidable and under present circumstances the exclusion from school of home contacts is quite futile. Sooner or later practically everyone suffers from an attack of measles. Almost all elementary schoolchildren are attacked before they leave school and it is a distinct asset for them to be immune to a disease so frequently epidemic. It is well known, though seldom taught, that the case-mortality of measles is low. In an epidemic in Brighton there were 30 deaths in 2402 cases. The mortality is high from 6 to 12 months, highest from 12 to 24 months, and diminishes rapidly in second, third and fourth years. The incidence is low in the first year but rapidly increases thereafter up to school age. Even when exposed to infection, young infants frequently escape attack. However serious the case and however poor the home, the child will do better there than in the ordinary hospital ward, owing to the rapid dissemination throughout the latter of organisms giving rise to fatal broncho-pneumonia.—D. Forbes, *Lancet*, ii/1933, 253.

In the common and fatal broncho-pneumonias and empyemas following measles in camps, *S. hæmolyticus* was found constantly. The importance of carriers of this organism in measles wards cannot be over-estimated. Cole found 11·4% of measles cases carried it on admission, 38·6% after 4 days, and 56·8% after 8 to 16 days. Cause of measles entirely unknown.—Stitt.

A review of recent work on measles.—J. E. McCartney, *Lancet*, i/1927, 93-97.

Mediterranean fever. Eruptive Mediterranean fever occurs along the Mediterranean coast of France and in Italy, Spain, Portugal, Greece, Rumania, Morocco, Algeria, Tripoli, Egypt and Syria. It is transmitted to man by the bite of a tick, *Rhipicephalus sanguineus*, found on dogs during hot weather. The tick bite usually occurs on parts of the body covered by clothing, and

causes a dark brown puncture 4 mm. to 10 mm. wide, described as the "black spot," the discovery and recognition of which is the most important point in diagnosis. The fever may begin sharply with rise of temperature to 101° or 102° , or slowly, reaching 101° on the third day, the patient complaining of headache, and joint, bone and muscle pains. Pulse regular at about 100, tongue slightly coated, vomiting may occur, some difficulty in swallowing and injection of conjunctivæ. Rash appears on the second to fourth day, comes out first on the trunk and limbs and spreads in 48 hours to the whole of the skin surface. It forms slightly raised, round or oval maculæ separated by areas of normal skin. These are pink at first, becoming red and then purple. The pharynx is red and slightly swollen, and the soft palate often shows maculæ. Temperature begins to fall when eruption is complete. Spleen and occasionally the liver are increased in size. Urobilin and sometimes bile found in the urine. Constipation usual. By the 5th or 8th day fever falls to 99° or 100° , where it remains for 3 or 4 days and then falls by lysis to normal on the 12th or 15th day, when the rash fades and disappears. The scabs of the tick bites come off between the 8th and 10th day. Convalescence is gradual, and weakness continues for some time. The disease has a favourable prognosis with mortality rate of less than 2%, without relapses, and with subsequent immunity. Diagnosis can be confirmed by the Weil-Felix reaction, i.e. by demonstrating the presence of agglutinins against *B. proteus* X 19 in the patient's blood. Reaction negative during febrile period but positive following fall of temperature. It resembles other eruptive fevers in various parts of the world, but is specifically different and has less grave prognosis.—A. Lemierre, *Lancet*, i/1934, 441.

Pellagra. Pellagra is a disease of long duration, characterised by a peculiar rash, not unlike a severe sunburn, which appears on the face, round the neck, and on the back of the hands and feet. This eruption recurs each year at determinate seasons (spring and autumn); it appears suddenly under the influence of exposure to sunlight, stands out some days, then fades off gradually, and is followed by long persistent desquamation. Together with the eruption other symptoms appear. They are irregular fever, frequent fits of giddiness with a peculiar sensation of falling backwards or forwards, great debility, confusion of mind, copious salivation, insomnia, pyrosis and diarrhœa. These symptoms abate during the summer months and disappear almost entirely in winter, especially in early cases. They return with the rash each spring. After a period of progressive aggravation, which may last 3, 5, or 30 years, the patient becomes greatly emaciated, partly paralysed, and entirely demented. A number of these unfortunate beings commit suicide, as a rule by drowning; the majority end their days in the lunatic asylums of their respective countries. The disease affects the agricultural classes almost exclusively.

The most constant and arresting symptom is progressive and extreme cachexia, with conspicuous loss of muscle and fat. In 65% of 74 cases treated at Tashkent (Central Asia) the first symptoms were digestive disturbances, diarrhœa and sore tongue. Stomatitis occurred in half the cases. The whole alimentary canal was in time attacked, from mouth to anus. In 25% diabetes insipidus coexisted with diarrhœa and cachexia. Mortality was 25% and treatment did little good.—J. Kassersky and L. Burova, per *Brit. med. J.*, ii/1932, 849.

Aetiology. The case seems settled in favour of a dietetic theory, and a theory which seems to fit the known facts may be formulated as follows: Pellagra is caused by a toxic substance derived from the maize diet, which can be corrected by sufficient "good" protein, or perhaps by sufficient vitamin B₂ (which is found to accompany the good proteins). The occurrence of pellagra in the U.S.A. among severe alcoholic addicts is possibly connected with the fact that illicit liquor may largely consist of "corn whisky" distilled from maize products, and the habit of the alcoholic addict to take little other food during periods of excessive indulgence would explain the failure to neutralise poisons derived from the maize liquor. In Rumania (where pellagra is a prevalent disease, maize is frequently the staple cereal, and "whisky" is often distilled from maize), the idea of an association between pellagra and the excessive consumption of alcohol is widespread both among the medical profession and the laity.—Harriette Chick, *Lancet*, ii/1933, 341.

From a pathological point of view there is apparently an intimate association between alcoholism and pellagra.—*J. Amer. med. Ass.*, i/1928, 371.

Pellagra can be prevented at will by the addition of any one of several known articles of food to the dietary, and can be produced at will by the removal of these items from the diet. The conclusion that the disease is due to a specific dietary fault is inevitable.—G. A. Wheeler and W. H. Sebrell, *J. Amer. med. Ass.*, ii/1932, 95.

Description of pellagra in a Sudanese community of millet-eaters. Data from 103 cases. In the period of maximum incidence of pellagra, the hot dry season, the community's main protein, cholesterol, and vitamin supply sinks to a practical deprivation, millet alone remaining as a food item. The fundamental condition is a lack of vitamins A and D, lack of C being contributory; pellagra is largely allergic and the evils resulting from cholesterol and vitamin deficiency contribute to the syndrome, as do also cereal toxamin effects. Pigmentation is protective against the actinic and tactile traumata affecting the skin of pellagrins.—N. L. Corkill, *Lancet*, i/1934, 1387. See also P. Ghalioungui, *ibid.*, ii/1934, 164.

Suggested that the relationship of diet to pellagra is primarily due to a specific quality of the amino-acid make-up of the protein supply.—J. Goldberger, per *J. trop. Med. (Hyg.)*, 1922, 220.

UNBALANCED DIET NOT THE ONLY FACTOR IN AETIOLOGY. The food factor, in lowering resistance, is an important predisposing cause. A full diet, rich in vitamins B and C, with low carbohydrate content, eliminating cane sugar, essential. Probably due to infection of some kind, when in condition of lowered resistance due to under-nourishment.—Seale Harris, *Int. Conf. Trop. Amer.*, 1924; 719. C. C. Bass opposed to the theory of diet as factor. Experimental pellagra in monkeys occurs in well-fed and well-nourished animals. He is convinced that it is infectious. Most cases get well spontaneously, and this has probably misled many.—*ibid.*, 720.

Pellagra is due to toxic absorption producing changes in nervous system, followed by neuritis of certain peripheral nerves, which produces trophic changes in areas of skin supplied by affected nerves.—Per *J. trop. Med. (Hyg.)*, 1926, 51.

A review of researches on ætiology.—*J. Amer. med. Ass.*, ii/1925, 212.

Pellagra is related to, but not caused by, poverty or under-nourishment, neither can it be ascribed to eating maize, or to avitaminosis.—J. Kassersky and L. Burova, per *Brit. med. J.*, ii/1932, 849.

Incidence. Pellagra is found in Europe, Africa, Asia, America, and even in Oceania, and probably affects more or less seriously over a million people.

IN THE U.S.A. it has an astonishingly high incidence (170,000 cases in 1917; 120,000 cases in 1927; mortality rate about 40%).—L. J. Harris, *Brit. med. J.* ii/1933, 232.

In the U.S.A. during 1930, 7146 deaths were recorded and for each death there were not less than 35 cases. 97·9% of the deaths occurred in the cotton belt. Pellagra has never been a problem in the strictly urban centres.—G. A. Wheeler and W. H. Sebrell, *J. Amer. med. Ass.*, ii/1932, 95.

IN GREAT BRITAIN. An account of four cases with description of the histological changes in the nervous system, also a history of the disease. The disease has been shown to be endemic to a limited extent, at least in some of the eastern districts of Scotland north of the Forth.—C. R. Box and F. W. Mott, *Brit. med. J.*, ii/1913, 1. May become epidemic in asylums.—A. D. Bigland, *Lancet* ii/1923, 1295.

Pellagra in children in England. Diagnosis, except in typical cases seen during spring and summer months when the rash is well marked, is not easy. Probably a number of cases go undiagnosed. Nothing in the history to fit in with the various causation theories of pellagra. Both children in question had been fed on large quantities of "Cornflour." Good reproduction plates of rash. Pellagra ought to be borne in mind, especially in cases of diarrhœa with occasional dermatitis in children.—R. Hutchison and D. Paterson, *Brit. med. J.*, ii/1923, 646, 670.

Treatment. Treatment of 28 cases by addition of tomato juice, raw cabbage lettuce, and water in which vegetables had been cooked, to the daily diet: complete cure of all the patients.—*J. trop. Med. (Hyg.)*, 1924, 344.

Five or six lemons a day will cure the average pellagra case in a very short time.—J. N. Roussel, *J. Amer. med. Ass.*, i/1928, 371.

Good results (great amelioration of all the symptoms) in 97 cases with sodium thiosulphate, daily injections of 10 ml. of a 10% sterilised solution of the chemically pure salt, the number of injections varying from 10 to 60. No contra-indications and no complications.—I. Sabry, *Brit. med. J. Epit.*, ii/1932, 44.

Effect of diet deficient in vitamin B₂ on the dermatitis of pellagra studied in 10 patients on a diet of corn starch and lactose amounting to 2000 to 3000 calories a day. In 8 cases a definite improvement in the skin lesions seen in from 6 to 15 days in spite of rapid loss of weight and strength. Care should be taken in interpreting the improvement in the dermatitis of pellagra as an index of efficacious treatment or of favourable prognosis.—T. D. Spies, *Arch. Intern. Med.*, Dec., 1933.

Pellagra Prevention. By a few simple and inexpensive additions to the daily menu the annual death rate from pellagra in a state institution for the insane has been reduced from 6·2% of all inmates to as low as 0·1%, in spite of the fact that deaths from this disease in the state at large increased by 100%. Of 35 foodstuffs tested for their pellagra-preventive value by the Public Health Service, milk, fresh beef, canned corn beef, liver, canned salmon, canned haddock, tomatoes, turnip greens and canned English peas, have each been found sufficient to prevent pellagra when added in sufficient quantity to a pellagra-producing diet; dried beans and peas, eggs, canned spinach, green cabbage and canned string beans, less effective but valuable contributory sources; cornmeal, wheat flour, rye flour, oatmeal, molasses, cane syrup, sweet potatoes, mature onions, carrots, ratatagas, salt pork, lard, cottonseed oil, butter and gelatin have little or no value regardless of quantity used. Dried yeast and commercial wheat germ are valuable supplements, especially for emergency conditions.—G. A. Wheeler and W. H. Sebrell, *J. Amer. med. Ass.*, ii/1932, 95.

Plague. The *symptoms* of plague in man develop within a few days of infection and consist of fever, headache, giddiness, weakness with staggering gait, great prostration, and delirium. In 75% of the cases the lymphatic glands in the groin, armpits and other regions are inflamed, infiltrated and much enlarged constituting the "buboes," hence the name "bubonic plague" frequently given to the disease. In the remaining cases the lungs

may be primarily attacked (the "pneumonic" form), or a severe blood infection may develop (the "septicæmic" variety); in both of these, buboes are absent, or are a late development if the patient lives. Occasionally an eruption of pustules or carbuncles appears on the skin, a phenomenon frequently mentioned by the older writers, and abscesses may form in the buboes. The bubonic form is hardly infectious or even contagious but the pneumonic variety is highly infectious, owing to the presence of large numbers of the infective agent, the plague bacillus, in the expectoration, from which it is readily disseminated in the air. In some instances the patients do not appear particularly ill, and are able to go about, though such cases are liable to sudden death from heart failure.—T. R. Hewlett, *Nature, Lond.*, Dec. 23rd, 1911.

Out of 50,000 cases of plague in an epidemic in Manchuria only two or three undoubted bubonic cases were observed, all the rest were pneumonic. The duration of the disease was usually less than 2 days, and no cases in which bacteriological diagnosis was complete were known to recover.—Review of Tropical Diseases, *Practitioner*, ii/1913, 218.

The Local Government Board issued a memorandum by G. F. Newsholme at the time of the outbreak in England (1910). This draws attention to the infected eyes and thick drunken speech.

In addition there is the well-known tendency to "shouting" delirium and the patients' impulse to get out of bed and wander off, utterly heedless of their condition—as seen in the natives of India.

Bacteriology. *Pasteurella pestis* is a short fat bacillus. On staining with weak aniline dye it shows marked polar staining. Spores have not been demonstrated. Non-motile. Does not retain the stain when treated by Gram's method; grows well on usual media both at room and body temperature. Does not liquefy gelatin. Occurs in chains when grown in fluid media. Forms typical stalactite growths in bouillon and in presence of butter-fat, but must be kept undisturbed (Haffkine). Man is inoculated through the broken skin.

The bacillus produces alkali in its growth equivalent to 1.5% to 2.5% normal sodium hydroxide solution in 6 to 8 weeks. This effects arrest of growth, but not death of the bacillus.

In smears made at an early stage of the disease from the buboes, expectoration, or blood respectively in the three varieties of plague, the bacillus is present in enormous numbers, and the films show "polar staining," the centre being hardly stained at all; this is characteristic. In older lesions, peculiar, large, rounded or ovoid "involution" forms of the bacillus are met with. The organism is readily destroyed by heat (60° to 65° for 10 to 15 minutes), and by disinfectants. The plague bacillus is pathogenic for a number of animals, in addition to man—the rat, mouse, guinea-pig, rabbit, hare, ferret, cat, monkey, etc. In the United States the ground squirrels are attacked.—R. T. Hewlett.

Concerning the discovery of the plague bacillus.—E. Lagrang
J. trop. Med. (Hyg.), 1926, 299.

Cultivation. Observations on the plague bacillus show the susceptibility of this organism to atmospheric oxygen. If small numbers of bacilli are inoculated into broth made in the usual way, growth may fail to occur. This appears to be due to a process of oxidation occurring in the broth as the result of exposure to air after sterilisation. If the broth is made in the way recommended in a previous paper by the author (*J. Path. Bact.*, ii/1933, 257), the peptone being added in an early stage of preparation, this process of oxidation does not take place, and the plague bacillus is able to grow satisfactorily. Direct observations show that the bacilli are exposed in a thin layer on an agar plate to the action of air, particularly at 37°, they die off fairly rapidly. This can be prevented either by exposing the organisms to an atmosphere with an oxygen content of not more than 1%, or by adding blood, serum, or a reducing agent such as sodium sulphite to the agar. In broth prepared according to the author's formula no destruction occurs, apparently because the oxygen content of the medium at 37° is under 1%. The difficulties of cultivation on solid media may be surmounted by using 0.1% blood agar or 0.1% sodium sulphite agar. Without these additions no growth occurs unless heavy inocula are used. The curious observation was made that, even though in the absence of a protective reducing agent such as blood or sulphite the bacilli are rapidly killed by exposure to air, in the presence of such an agent growth occurs more profusely under aerobic than under anaerobic conditions.—H. D. Wright, *J. Path. Bact.*, ii/1934, 38; per *Brit. med. J.*, i/1935, 34.

Transmission. The flea, usually *Xenopsylla cheopsis*, is the transmitter from rat to rat and from rat to man.—*Lancet*, ii/1926, 632. Clinical experience shows that plague has no preferential temperature, though the Third Report of the Plague Commission sought to establish a "climatic plague temperature" of 85° to 50°F. Calcutta is remarkably free from human fleas; dog fleas are prevalent on the other hand, and rat fleas are seldom or never found. Rat fleas do not bite men, on the contrary they have a strong distaste for the skin of man. Evidence of equally conclusive nature in the opposite direction by a Member of the Commission. There is always an association between rats and plague in India.

Varieties of rat fleas spreading plague.—*Lancet*, ii/1921, 1287.

Transmission of plague by fleas. *Xenopsylla astia* probably the sole rat flea relatively immune to plague.—L. Fabian Hirst, per *J. trop. Med. (Hyg.)*, 1924, 114.

Bubonic plague is a disease of rats, and the human case is, for all practical purposes, not infectious. Abundant evidence that bubonic and pneumonic plague are entirely separate and distinct epidemic diseases. It is doubtful whether plague bacillus alone can cause pneumonic plague epidemics, which are probably caused by the bacillus in symbiosis with another organism, probably non-pathogenic for rodents. Control of grain trade and the proper storage of grain in "rat-free" stores almost synonymous with efficient plague preventive measures. Disinfection of houses, etc., the most common of all anti-plague measures, excites great antagonism and is of doubtful value. Attention paid to the usual channels of infection could secure almost absolute immunity from plague, without restriction to the free flow of commerce.—N. White, Report to Health Committee of the League of Nations, per *Trans. R. Soc. trop. Med. Hyg.*, 1924, 525.

Evidence is conclusive to incriminate the Asiatic tarabagan, or bobac, as the carrier of pneumonic plague.—*Lancet*, ii/1924, 330. *Arctomys bobac*, known in England as the marmot, in Russia as the tarabagan, and in China as the hanta, is the rodent which was held responsible for the plague in China (1910-11). 19th Edn., Vol. II, p. 564.

Plague sputum is extremely resistant to carbolic, lysol, sublimate, potassium permanganate, hydrogen peroxide, alcohol, methylated spirit, etc. Pneumonic plague is a direct infection from man to man. Infection is carried in droplet form—when sputum is thrown out during coughing, talking, etc. Crushed sulphur burnt, after the walls have been sprayed with water, is best for fumigating houses. Floor containing sputum covered with slaked lime. Clothes :

overalls fumigated with formalin gas made by warming 100 g. of permanganate, 100 g. of hot water and 200 g. of formalin in a pot.—G. L. Tuck, *Lancet*, ii/1921, 853.

PLAGUE IN MANCHURIA. *P. pestis* present in plague sputum killed within 9 hours by direct sunlight at a winter temperature ($=3^{\circ}\text{C.}$). Phenol lotion 1 in 10 requires 5 minutes to prevent growth of *P. pestis* in sputum.—W. L. Teh, *J. trop. med. (Hyg.)*, 1923, 256.

PLAGUE IN ASTRAKAN. Camels an important source of infection in man owing to their eating hay and green fodder infected by mice and ground squirrels.—S. M. Nikanorov, per *J. trop. Med. (Hyg.)*, 1923, 128.

PLAGUE IN BAGHDAD. It is endemic in that district and is determined by climatic conditions.—T. B. Heggs, *J. trop. Med. (Hyg.)*, 1923, 328.

Pneumonic plague in Iraq.—T. B. Heggs, *Proc. R. Soc. Med.*, 1924, 45.

PLAGUE IN EGYPT.—A review of its past and recent history.—*Brit. med. J.*, i/1924, 582; *ibid.*, 900.

PLAGUE IN INDIA. During the years 1898-1918 plague carried off a total of 10,254,221 people—an annual average of over half a million.—*Indian med. Gaz.*, 1925, 277.

Treatment. Haffkine's Plague Prophylactic (Plague Vaccine of the Lister Inst.) Haffkine's vaccine is prepared from a 2 to 6 weeks' culture of *P. pestis* incubated at 25° to 30° in goat digest broth, killed by heating for one hour at 65° ; 0.5% phenol is added to maintain sterility (Topley and Wilson).

After injection there is a local swelling and probably general malaise and heightened temperature. *Immunity* is conferred after 7 or 8 days by an injection, and it is advisable to inoculate persons exposed to infection every six months.

Dose: 4 ml. for adults or 3 ml. when administered within 3 months of date of manufacture, subcutaneously in any loose tissue free from veins, e.g., the flank.

Since 1896 the Bombay Bacteriological Laboratory has issued 25 million doses of Haffkine's vaccine. Statistics show a reduction in mortality by prophylactic injection of this vaccine of about 47%, in addition to which fewer persons contract plague among the inoculated than among the uninoculated. Several million lives have been saved by the use of this vaccine.—*Indian med. Gaz.*, June, 1925, 284.

A record of analyses of more than 300,000 persons of whom 40% were inoculated, exposed to plague risk shows that Haffkine's vaccine gives approximately a fourfold protection against attacks of plague and an eightfold protection against death.—J. Taylor, *Indian med. Res. Mem.*, March, 1933, per *Brit. med. J.*, ii/1933, 66.

A new anti-plague serum prepared by the Haffkine Institute (Bombay) from cattle (bullocks and buffaloes) using a highly virulent strain of *P. pestis*, shown far superior to any other anti-plague serum tested. Of a series of 76 cases, 43 treated with the serum showed 14 deaths, while of 33 controls treated without serum, 23 died.—B. P. Naidu and D. P. H. Brist, *Lancet*, ii/1931, 896.

Yersin's Curative Serum (also used as a prophylactic) is supplied in 20 ml. bottles.

Dose: At the earliest possible moment 50 ml. intravenously and 50 to 100 ml. intramuscularly or subcutaneously, e.g., in the flank, repeated in 12 to 24 hours. 20 ml. is given as a preventive.

Injection of Yersin's anti-plague serum may give rise to urticaria accompanied by rise in temperature, faintness and pain may follow. Rest and abstinence from alcohol are essential.—Luisi, *Trop. Dis. Bull.*, 1922, 734.

In 1908-9, 1491 cases of bubonic plague were treated in Guayaquil, Ecuador. Patients not receiving anti-plague serum gave death-rate of 60%, as against 33% of those who received it. Where treatment could be given within 24 to 36 hours of onset, mortality might be reduced to 18% or 20%. Fresh serum essential.—B. J. Lloyd, *J. Amer. med. Ass.*, ii/1925, 731.

Bacteriophage therapy should constitute the specific treatment for plague, from 1 to 2 ml. of a very virulent bacteriophage culture being injected as soon as possible. Four cases of bubonic plague recovered rapidly following injection into the buboes.—F. d'Herelle, *Pr. Med.*, Oct 21, 1925, per *J. Amer. med. Ass.*, ii/1925, 1653, 1762.

Pneumonia

Fraenkel's Pneumococcus. 1. Prepare films from "rusty" portion of sputum. 2. Stain by Gram's method and counterstain with eosin $\frac{1}{2}$ to 1 minute. Stain other films by carbol-fuchsin. Overstain (5 minutes). Slightly decolorise with weak acetic acid. (For capsule.)

To obtain a pure culture, the blood of a mouse dead from inoculation of sputum is sown on blood agar or Nasagar medium. Will not grow below 37° .

Recognition.—Diplococcus (ends are often pointed—*Diplococcus lanceolatus*) sometimes occurs in short chains of four to ten cocci. Has a capsule, but this is absent in cultures. Gram-positive.

This organism is the cause of more than 80% of lobar pneumonia.

Sterile broth extracts of unwashed pneumococci, free from living or intact cells, actively reduce methylene blue.—*J. trop. Med. (Hyg.)*, 1924, 346.

The soluble specific substance of pneumococcus. Weight evidence is in favour of view that specific substances of pneumococcus Types II and III are actually polysaccharide derivatives.—*J. trop. Med. (Hyg.)*, 1924, 346.

Pneumococcal infections—the bacteriological aspect.—J. H. Dible, *Lancet*, i/1924, 8.

Growth of the Pneumococcus: Sir A. E. Wright's Serum Glucose Broth. 1% peptone, 1% lemco, $2\frac{1}{2}\%$ to 5% of human serum and an amount of alkali fixed by neutralising to phenolphthalein and then adding 6 ml. of normal acid to each litre of medium. 1% glucose was found a valuable addition—the broth so made gave copious growth of pneumococci.—*Lancet*, i/1914, 111.

The best medium for differentiating is the serum of a young rabbit, in which it grows as a diplococcus, while streptococci show chains. On plain agar it grows as a very small dew-drop-like colony; slightly greyish by reflected light. It produces considerable acid and coagulates litmus milk. Acid is produced in inulin media which streptococci fail to do. The most important differentiating point is its solubility in bile.—Stitt.

In cataract cases (at Prague) examination for pneumo- and streptococci. Growth in **Elschnigs' Culture Medium** (1 part horse serum and 3 parts bouillon without peptone) is made and if found operation postponed with hourly applications of 1 in 5000 mercury oxycyanide solution until the organisms have disappeared. Simultaneously an agar culture is made for identifying staphylococci if present.—E. W. Thomson, *Glasg. med. J.*, Feb., 1911.

CONJUNCTIVITIS, BACTERIOLOGY OF. In a school outbreak an organism morphologically identical with the pneumococcus but differing in fermentative activity and its non-pathogenicity to animals, usually highly susceptible.—*Lancet*, ii/1911, 1418.

Immediate Pneumococcal Typing. Place three small samples of sputum on a slide, equidistant and numbered 1, 2 and 3, each sample being emulsified with four times its volume of the corresponding diagnostic serum, apply cover glasses. Take a further sample from the same fleck of sputum, fix by heat and stain by Gram's method. The general bacterial flora of the sputum and the number of pneumococci present are apparent at a glance in the stained film, which exactly represents the characters of the sputum samples selected. Examine

slide with emulsions, using a 4-ocular 1/6 objective, and plane mirror, the condenser being removed. Whereas the unstained pneumococci when present in small numbers are but just visible in the case of a negative test, in the case of a positive reaction there is a conspicuous increase in size of the individual pneumococcus, with a characteristic ground-glass appearance and a highly refractive peripheral zone. The positive, when compared with controls on the same slide, is seen to be opalescent. When the pneumococci are thickly coated with sero-mucinous pneumonic secretion full development may take 20 minutes.—R. R. Armstrong, *Brit. med. J.*, i/1932, 187.

Make a saline emulsion of the sputum. Mark four slides 1, 2, 3 and control, and place a large loopful of the undiluted type serum on the appropriate slide, and a drop of saline on the control. Place a drop of the sputum emulsion beside each drop of serum and mix. Use a 1/12 oil-immersion lens, plane mirror and bright artificial light. When pneumococci are present in large numbers the swelling of the pneumococci and the appearance of the dark line sharply outlining the capsule, with a darkening of the body of the pneumococcus itself, are very strikingly seen when the homologous serum has been used. Owing to unequal distribution of the pneumococci through a sample of sputum the test may have to be repeated several times. Of value to a bacteriologist but should be confirmed by typing of a pure culture.—W. R. Logan and J. T. Smeall, *Brit. med. J.*, i/1932, 188.

A Staining Method for Direct Typing of Pneumococci. Mix three or four loopfuls of type I serum on a slide with a loopful of sputum, and mount with cover-glass (similarly with types II and III sera), the edges of which are sealed with vaseline; leave for 20 to 30 minutes, then take off cover-slips, allow the films to dry and scrape off most of vaseline. Wash under tap to remove serum, stain for 2 or 3 minutes with dilute carbol fuchsin (stain freshly diluted with 5 or 6 parts of water), wash and counterstain for 10 seconds with carbol thionin (9 parts 5% phenol in water and 1 part 50% alcohol saturated with thionin).

The bodies of all bacteria stain practically black and everything else is red. The capsules of pneumococci treated with the homologous serum appear quite large and stain a strong red, while the "unneutralised" capsule does not stain.—F. C. O. Valentine, *Lancet*, i/1933, 22.

Antipneumococcus Serum, Types I and II.

Standards. International standards for both these sera have been prepared in the form of dried sera, and units have been defined in terms of the activity contained in a given weight of each.

The units have been adjusted so as to be as nearly as possible identical with the Felton units for these two sera. The Felton unit for each serum was defined as the activity in a quantity of liquid serum, but since the activity was slowly deteriorating, the Felton unit was a varying unit. The introduction of the international standards of dried serum has stabilised the unit.

All forms of antipneumococcus serum types I and II, and mixed sera containing antibodies against other strains, must comply with regulations (S. R. & O. 1935, No. 580) made under the Therapeutic Substances Act, 1925. Standard preparations are issued by the National Institute for Medical Research, and the units are the quantities of the standard preparations equivalent to the international units.

The methods of standardising samples of the two sera are very similar and depend on the protective power of the sera for mice infected with a dose of living virulent pneumococci of the corresponding type. In carrying out a test, large numbers of mice are required; for example, 60 mice may be infected by intraperitoneal injection with 0.01 ml. of the culture of living pneumococci; of these, 30 receive an intravenous injection of the standard serum, and 30 receive an injection of the unknown serum. If the unknown serum is equal in potency to the standard, the proportion of mice in each group which do not die will be the same. Tests are repeated until the same proportion of mice (usually 50%) is protected by the dose of the unknown serum as by the standard serum.

A concentrated serum prepared by Felton's methods is made by immunising horses against type I or II and is concentrated by separating the protein fraction which contains the protective antibody. It is titrated in terms of a unit which is defined as the smallest amount of serum which will neutralise 10^7 lethal doses of a virulent pneumococcus culture when the test is performed on mice under prescribed conditions.

Huntoon's antibody solution contains immune bodies against types I, II and III. The method of preparation is first to absorb the antibody from a specific serum by adding to it living pneumococci, and afterwards to effect a separation of the antibody by washing the coccal deposit in a weak alkaline solution. The clinical results from its use seem to have been satisfactory. Intravenous use is often followed by severe reaction, although it *contains no horse serum protein*.

Friedlander's Pneumobacillus, *syn. B. mucosus capsulatus*. Present in only small proportion of cases of pneumonia. Common in influenza. Gram-negative, but stains well with carbol fuchsin.

Recognition.—A bacillus varying considerably in length; usually short with rounded ends. Non-motile, usually $1 \times 2.5 \mu$. Has a capsule. Is easily cultivated on all ordinary media.

Produces gas in glucose media, but not in lactose bouillon; differentiation from *B. coli*. In a gelatin stab it presents a "nail" appearance, the growth at the surface being heaped up like a round-headed nail and the line of puncture resembling the shaft. It is best examined by dark ground or parabolic illumination. Stain by Gram's method but do not wash with alcohol and omit any counterstain. Hot acid-fuchsin gives good results.

The organism is the probable causal agent of pseudo-membranous bronchitis, chronic bronchitis and pseudo-pneumonia.—*Brit. med. J. Epit.*, ii/1927, 79.

The source of the Pneumococcus and Modes of Infection, Pneumococcus Vaccine, Prophylactic Inoculation, Types of the Pneumococcus and Serum are dealt with Vol I, p. 916, et seq.

Poliomyelitis. (Inflammation of the grey matter of the spinal cord.)

Three clinical stages of evolution of poliomyelitis—general infection, during which the virus enters the liver, spleen and lymphatics, invasion of the subarachnoid space, and thirdly invasion of the central nervous system itself, this last phase producing paralysis. During the second stage the cerebrospinal fluid gives a meningeal reaction and its cell count ranges from 30 to 2000 cells per c.mm. The blood reveals a leucocytosis in most cases, the total white cell count rising as high as 25,000 with a relative predominance of polymorphonuclear cells.—F. M. R. Walshe, *Lancet*, i/1927, 326.

A good series of clinical pictures of poliomyelitis.—J. Collier, *Lancet*, i/1927, 321.

The evidence presented on the mode of infection has established two important facts: first that the disease is a particular form of infection of the upper respiratory tract; and secondly that the cases arising during an epidemic cover a wide latitude in degree of symptoms and pathological effects. There is a consensus of opinion that the number of children suffering some degree of infection is many times as great as the number that are frankly paralysed. The wide occurrence of the slighter forms of infection can be taken as a means of delimiting the prevalence of the severer affection, since experimental observations have shown that *any* degree of actual infection protects inoculated monkeys from the effects of a second administration of the virus.—S. Flexner, *Brit. med. J.*, i/1933, 133.

Ætiology. There seems to be general agreement that the causal organism of poliomyelitis is a virus gaining access through the nasopharynx and undergoing an axonal transmission. Faber and Gebhardt have, in fact, experimentally traced the course of the virus, after intranasal inoculation, from the olfactory

bulb to the cells of the spinal cord, and the first-named has shown that the symptomatology in man can be explained on the hypothesis of a primary nervous infection.—*Brit. med. J.*, ii/1934, 863.

The most refined microscopic technique fails to reveal regularly any definite micro-organism in the nervous tissues and even in cultures treated in the most painstaking manner. The agent producing experimental poliomyelitis belongs to the filter-passing class. The virus, once it is adapted to the monkey, is incredibly active, and may be passed by inoculation from animal to animal indefinitely. At the Rockefeller Institute a virus has been passed for 20 years and its activity is still unimpaired. The virus escapes and is put into circulation exclusively by way of the secretions of the nasopharyngeal mucous membrane.—S. Flexner, *J. Amer. med. Ass.*, i/1928, 24.

Epidemiology. Infection may be conveyed by (1) persons suffering from an acute attack, (2) persons having a mild or a typical form, (3) healthy contacts who have not developed an attack, and (4) chronic carriers who have apparently recovered from a previous attack.—A. S. MacNalty, *Lancet*, i/1925, 478.

In 1918, 228 cases were notified in England and Wales, the larger proportion being between 1 to 5 years old. Usually one attack produces permanent immunity. The incubation period appears to be from 2 to 10 days.—*ibid.*, 536.

Treatment. Convalescent serum (serum from patients convalescing from an acute attack).

Intramuscularly of distinct value, its effectiveness depending on early diagnosis and injection of sufficiently large and, if necessary, repeated doses. Owing to its safety and simplicity it can be used in doubtful cases.—*Brit. med. J.*, ii/1928, 501.

Directions for the collection and preservation of convalescent poliomyelitis serum.—S. Flexner, *J. Amer. med. Ass.*, i/1928, 24.

The Medical Research Council, after discussion with the Ministry of Health, the Public Health Dept. of the L.C.C., and the Lister Institute, has decided to issue a supply of convalescent serum with a view to its trial in the pre-paralytic stage of the disease, as adequate data are still needed to confirm its value. A limited supply has been obtained and prepared for use by the Lister Institute and the main stock deposited at the Western Fever Hospital, Seagrave Road, London, S.W.6. Outfits containing 25 ml. (sufficient for one case) are supplied gratuitously, for use only in the pre-paralytic stage, to practitioners experienced in the technique of lumbar puncture and intrathecal injection.—*Brit. med. J.*, ii/1933, 71; see also *Lancet*, ii/1934, 884. (These outfits are still available—1935.)

The following sera have also been used:—

Immune Serum (serum from patients who have had an attack any time previously).

In New Zealand, Canada, Australia and the U.S.A., experience has led many workers to consider human immune serum a therapy of value in promoting prompt recovery and protecting from severe paralysis.—J. Macnamara, *Brit. med. J.*, i/1933, 527.

Serum from normal adults with no history of the disease.

Antistreptococcus Serum. A streptococcus having peculiar neurotropic and immunologic properties has been cultivated from the throat, brain, cord and spinal fluid in cases of typical poliomyelitis. It has unmistakeable curative action and results obtained compare favourably with those reported from the use of convalescent serum.—E. C. Rosenow, *J. Amer. med. Ass.*, i/1930, 777.

Antiviral serum of marked activity against the poliomyelitis virus has been produced by the intramuscular inoculation of the living virus in horses. The serum has been used in a few cases in this country but it is not possible so far to draw any conclusions as to its efficacy.—R. W. Fairbrother and W. T. J. Morgan, *Lancet*, ii/1931, 584.

Recent work has thrown doubt on the possibility of influencing the course of poliomyelitis by the administration of serum. Meanwhile, investigators are turning their attention to specific prophylaxis, and most is to be hoped from a method of active immunisation which is both effective and yet safe enough to be used in man.—*Lancet*, i/1935, 686.

A vaccine consisting of a 4% suspension of poliomyelitis monkey cord in 1% sodium ricinoleate and stored for one month at 10° (to allow for maximum

attenuation of the virus) is claimed to give good results from the standpoint of antibody production. Twenty-five children varying in age from 8 months to 15 years were given the vaccine subcutaneously, the dosage varying from 0·25 ml. to 0·5 ml. for children under 2, older children receiving an initial dose of 0·5 ml. and a total of 2·0 ml. to 3·5 ml., three doses being given at weekly intervals.—J. A. Kolmer, G. E. Klugh and A. M. Rule, *J. Amer. med. Ass.*, i/1935, 456.

Poliomyelo-encephalitis (poliomyelitis and polioencephalitis existing together) in which the lesion chiefly or solely involves the upper motor neuron, giving rise to spastic paralysis, is a rare disease, but has also been described.—A. S. MacNalty, *Lancet*, i/1925, 537.

The use of human immune serum in the preparalytic stage gives excellent results (low mortality rate, low average total paralysis, and strikingly low proportion of severe paralysis). Initial dose rarely less than 50 ml. intravenously, delay between withdrawal of cerebrospinal fluid and injection of serum being avoided. Examine patient at 12, 18 and 24 hours later—if dose adequate, temperature falls and general condition greatly improves. After injection of serum give brisk aperient and carbohydrates and fluid freely. If no marked improvement in 18 hours give a further 30 ml. to 40 ml. intravenously. Review of 270 cases treated at Melbourne.—J. Macnamara and F. G. Morgan, *Lancet*, i/1932, 469–472, 527–532.

Psittacosis (Parrots' Disease) Characterised in man by an atypical pneumonia, weakness and depression, and signs of a profound infection. Time of incubation about 10 days, the symptoms being headache, fever, anorexia, restlessness, delirium, vomiting, diarrhœa and albuminuria, broncho-pneumonia sometimes supervening. Death occurs in about one-third of cases. Disease more common than is supposed—erroneous diagnosis easily made.—per *Prescriber*, 1929, 308. Due to a filtrable virus—work at London Hospital.—*Brit. med. J.*, ii/1930, 535.

History, case records, clinical signs, incidence.—A. P. Thomson *Lancet*, ii/1929, 115.

A study of 27 cases, 5 of which died. Prior to the 1929–30 epidemic, practically unknown in this country. The town of Cordova (Argentina) had numerous cases in 1929. Cases in this country connected with green Amazon parrots. Incubation period 8–13 days. Lungs involved in all cases. A typhoid-like state developed; sometimes incessant vomiting; pulse slow in relation to temperature; latter very high from the onset.—R. Hutchison and co-workers, *Brit. med. J.*, i/1930, 633.

3 cases with 2 deaths.—H. R. Fisher and R. J. Helsby, *Brit. med. J.*, i/1931, 887. Summary of necropsy.—D. S. Russell *ibid.*, 888.

Two human cases came to notice in England and Wales during 1933. Though parrots are the most usual conveyors of the disease to man, parakeets and other birds are often a source of danger and as parakeets are extensively bred in this and other temperate countries, human psittacosis is likely to occur if infection is introduced among the birds of a breeding aviary. In the U.S.A. during 1932 there were 76 cases with 7 deaths, and in 1933 11 cases with 4 deaths—nearly all the cases due to home-bred parakeets. Similar cases have occurred in Germany recently.—*Rep. med. Offr Minist. Hlth, Lond.*, 1933, 50.

Rabies. HYDROPHOBIA is an acute infectious disease communicated to man by bites of animals suffering from rabies. Cauterise the bite wound with strong nitric acid as quickly as possible, even if the Pasteur vaccine can be given.

In man the incubation period after infection is usually about 40 days, but varies from 15 days to 7 or 8 months.

Cultivation. H. Noguchi, by the method used for isolating the spirilla of recurring fever, isolated two forms of micro-organism from cultures prepared from the brain or spinal marrow of animals infected with hydrophobia. One is a minute corpuscle almost ultramicroscopic, the other, which is constantly reproduced in successive cultures, a larger nucleated corpuscle which more resembles protozoa than bacteria. These nucleated corpuscles multiply rapidly both by budding and fissure. They vary from 1 to 12 microns and by the ultramicroscope show a central nucleus surrounded by a very distinct refringent membrane. Inoculation with cultures, in which either the granular or the pleomorphic organisms predominated, caused the death of the animal with all the typical symptoms of rabies.—*Pr. méd.*, 1913, per *Pharm. J.*, i/1914, 219.

Treatment. Antirabic Vaccine. A dead carbolised rabies virus made by Sir David Semple's method can be sent to any locality, where treatment can be carried out, without losing its properties.

A central institute could supply the whole of India with vaccine, patients would hence be saved long journeys to Pasteur Institutes where the preparation of living vaccine is carried on. Most important of all, the treatment would be early—this is the essence of success, and the treatment is free from all risks.—Sir D. Semple, *Sci. Memoirs by Officers of the Med. and San. Dept. of the Indian Govt.*, 1911; also *Lancet*, ii/1911, 173.

Rabies and antirabic treatment.—Sir D. Semple, *Brit. med. J.*, ii/1919, 333, 371.

A rapid method of antirabic treatment by etherised vaccine.—*Brit. med. J. Epit.*, ii/1925, 14.

Good results obtained by *intravenous* injection of antirabic vaccine. Rate of injection should not exceed 0.5 ml. a minute, the dose being 2 ml.; there are no local or general symptoms following use. 96 cases treated, with 5 to 7 doses intravenously, with one death. Treatment may be regarded as safe.—*Brit. med. J. Epit.*, i/1925, 2.

Immunisation. Two Japanese workers—Umeno and Doi—introduced a method of immunising dogs by a single injection. The vaccine is prepared from the brain and cord of a rabbit dying from a laboratory strain of rabies which kills the animal in 7 days, i.e., a "fixed virus." To the ground-up nerve tissue is added 4 times its volume of a phenolised glycerin-saline solution, and the mixture kept for a month in an ice-chest to reduce its virulence; it keeps for two or three months at room temperature. In Japan over 30,000 cases have been vaccinated with only one failure, and in the areas where it has been used rabies has been reduced already by 75%. Equally successful results obtained with the vaccine in U.S.A.—*Brit. med. J.*, i/1924, 1060.

The comparative immunising value of carbolised, etherised-carbolised, and etherised vaccines. A 5% carbolised dead vaccine now recommended in place of the Alivisatos etherised vaccine previously employed. Animal experiments leave little doubt that the *virus fixe* from the Pasteur Institute, Paris, has better antigenic properties than the Kasauli fixed virus which is in use in the majority of the Pasteur Institutes in India. The Paris virus should be substituted for the Kasauli fixed virus. There is strong evidence in favour of the periodic testing and distribution of a virus of standard strength from suitable central institutes.—J. Cunningham, R. H. Malone, and A. C. Craighead, *Indian med. Res. Mem.*, No. 26, Jan., 1933; see *Brit. med. J.*, i/1933, 979.

Relapsing Fever, syn. Recurrent Fever, is associated with the presence of *Treponema obermeieri* (syn. *Borrelia recurrentis*, *Spirochæta obermeieri*), in the blood. In cases of relapsing fever terminating fatally the blood is frequently found to be teeming with the organisms. The corpuscles with the $\frac{1}{12}$ in. oil immersion lens frequently appear to have slender spiral filaments attached to them, causing a rippling movement of the blood which persists for several hours when examined in the fresh condition. Wenyon mentions 12 species of relapsing fever spirochætes.

Wassermann reaction in relapsing fever. 11 out of 18 cases gave positive reaction. Transient positive reaction may be expected during acute stages of relapsing fever.—*Brit. J. exp. Path.*, per *J. trop. Med. (Hyg.)*, 1922, 264.

Cultivation. Noguchi cultivated four species of pathogenic spirochætes occurring in the blood (as distinct from those which invade tissues—*Sp. pallidum*, *q.v.*, and that of yaws), including *Sp. obermeieri* which is the cause of relapsing fever in Europe, and the spirochæte of the fowl.—*Brit. med. J.*, ii/1913, 1100.

S. Hata cultivated spirochætes of recurrent fever in a medium containing horse serum and buff coagulum. The virulence of the cultivated spirochæte is relatively weak. Sir Wm. Leishman showed evidence of granule-shedding in spirochætosis and the development of the spirochætes from the granule.—*Int. Cong. of Medicine*, 1913, *Lancet*, ii/1913, 569.

Kligler and Robertson (1922) found the following medium successful for the growth of relapsing fever spirochætes; horse or rabbit serum diluted with 1 or 2 parts of saline solution, or undiluted ascitic fluid; to each 10 ml. of this fluid is added 1 ml. 10% peptone broth; reaction adjusted to pH 7.2; place 3 to 4 ml. of the mixture in each test-tube. Inoculate with a drop of blood or 0.1 ml. fluid from a previous culture, and cover surface with a layer of oil. Aristowsky and Holtzer (1924) used a medium prepared by adding 8 ml. saline solution to 4 ml. young horse's serum in a test-tube and introducing a piece of blood-clot or white of hard-boiled egg; inoculate and incubate at 35°; subculture every 48-72 hours.—Wenyon, p. 1257.

Transmission. Infection in lice by the spirillum of recurrent fever is hereditary, contrary to previous views. The spirilla occur in the lacunary cavity of the insect, not in the mouth organs or digestive apparatus. Inoculation does not take place from bites but through wounds on the animals caused by scratching. The animals become infected with fluid from crushed lice conveyed by the nails.—*Ann. Inst. Pasteur*, per *Pharm. J.*, ii/1913, 729. A human being who had allowed himself to be bitten 30,000 to 40,000 times with infected lice never became infected, as care had been taken not to damage the insects. Only occasionally does infection pass through the eggs of lice to the succeeding generation.—Wenyon, p. 1253.

The so-called "**tick fever**" *q.v.* is due to *Treponema duttoni* and is transmitted by ticks, whereas the European, Asiatic and American forms of relapsing fever are transmitted by the body-louse.

Ringworm. The organism of *favus* is *Achorion Schonleinii*; those of *Tinea tonsurans* (RINGWORM OF THE SCALP) and *T. circinata* (RINGWORM OF THE BODY), i.e., non-hairy skin, are *Microsporon Audouini*, *Tricophyton Megalosporonectothrix*, and *endothrix* (according as the fungus lies outside or inside the hair); that of *Tinea versicolor* (PITYRIASIS) is *Microsporon Furfur*.

Tinea barbæ or *Hyphogenic sycosis* (RINGWORM OF THE BEARD) is a common affection of the beard. The common grey coccus inhabiting the upper layers of the epidermis may cause infection and pustulation, but the fungus can be distinguished from this coccigenic variety. Syphilis may also sometimes simulate

ringworm of the beard. *Eczema marginatum* is a name for ringworm attacking the groins and axillæ. *Onychomycosis* or ringworm attacking the nails only—not common, but very troublesome.

Staining. For permanent stained sections:—

- (1) Soak the hairs in potash solution for 10 minutes.
- (2) Stain with aniline gentian violet (q.v.) for 1 hour.
- (3) Absorb excess of stain.
- (4) Treat with Gram's iodine solution 2 minutes, wash in water. Decolorise with acidified aniline oil (aniline oil 10, nitric acid 1) for 15 to 20 minutes. Treat with aniline oil 1 minute, clarify in xylol, and mount in balsam.

Rapid clinical method of search:—

- (1) Soak the hairs in potash solution for 10 minutes.
- (2) Wash in water to free from alkali.
- (3) Mount in glycerin or glycerin jelly.

Cultivation of ringworm fungi is possible on all ordinary media, but the addition of glucose or maltose is most favourable.

Diagnosis. The trichophytin test for ringworm. 0.1 ml. of trichophytin (a protein extract of *Trichophyton*) is injected intradermally into the volar surface of the forearm. The reaction may be read at 24 and 48 hours. A positive reaction is generally accepted as indicating that the body is producing antibodies to destroy the fungus.

Rocky Mountain Spotted Fever resembles symptomically typhus exanthematicus. Supervenes on the bite of a tick, *Derma-centor venustus*.—Manson.

Potent immune serum against Rocky Mountain spotted fever can be produced in the rabbit. 16 ml. confers immunity to an average adult.—Hideyo Noguchi per *J. trop. Med. (Hyg.)*, 1923, 145.

Remarkable variation in case mortality. In Montana, fatalities are 90% of the case incidence, while in Idaho they are only 5%. Serum effective in reducing death-rate.—*Lancet*, ii/1928, 473.

Tick fever in America is synonymous with Texas fever and Rocky Mountain spotted fever, and the State of Montana (where, since 1914, spotted fever has occurred in 36 of 56 counties of the State) is attempting to get rid of the ticks by means of a specially-bred tick parasite, 120,000 of which are liberated weekly between April and July. A prophylactic vaccine made from infected ticks is distributed free by the U.S. Public Health Service, and is proving of value.—*J. Amer. med. Ass.*, i/1927, 1649; i/1928, 1049.

See also *Mediterranean Fever*, this volume, p. 573.

Scarlatina or Scarlet Fever. In most cases, with or without albuminuria, streptococci are voided by the urine in large quantities in this fever.

Various drugs, taken internally or used locally, may occasionally, especially where idiosyncrasy exists, produce scarlatina-form rashes, e.g., Venice turpentine, applied externally.

Bacteriology. No one serological form of streptococcus can be credited with causation of scarlet fever, although three or four, recognisable serologically, seem exceptionally commonly found in this disease. Power of causing scarlet fever is intensity of toxin production rather than any property discoverable by agglutination.—The Hæmolytic Streptococci: Their Grouping by Agglutination, F. W. Andrews and E. M. Christie, *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 169, 1932.

Mervyn Gordon pointed to three distinct types of hæmolytic streptococci.—*Brit. med. J.*, i/1921, 632; ii/1923, 772.

Gordon's Type III (*S. scarlatinæ*) is found chiefly in tonsils and fauces of scarlet fever patients and is quite distinct from the more common hæmolytic *S. pyogenes*. The work has been carried further by Coronia and Surdoin, who have conferred immunity on children, as also by Takahashi of Tokyo, and G. F. Dick and G. H. Dick.—*Brit. med. J.*, ii/1923, 772. See also Vol. I, p. 92.

The hæmolytic streptococci of scarlet fever resemble others in morphology. Their specific toxin can be recognised. Method of doing it is detailed (Dick's work).—*Brit. med. J.*, i/1925, 792.

Hæmolytic streptococci and scarlet fever. Can be differentiated from those of erysipelas, septicæmia, puerperal fever, etc., by agglutination methods.—R. A. O'Brien, *Brit. med. J.*, ii/1926, 513.

Preparation of scarlet fever streptococcus toxin of high potency.—R. A. Q. O'Meara, *Brit. J. exp. Path.*, 1934, 15, 295.

Two distinct scarlet fever streptococcal toxins described by S. B. Hooker and E. M. Follensby, *J. Immunol.*, ii/1934, 177.

Streptococcus toxin (scarlatina) is partially detoxicated by formaldehyde, but there is no evidence that a scarlet fever toxoid analogous to diphtheria toxoid can be produced.—G. F. Dick and G. H. Dick, *J. Amer. med. Ass.*, ii/1934, 1362.

Diagnosis

Schultz-Charlton Blanching Test. Ordinarily 0·2 ml. of streptococcus antitoxin (scarlatina) made in the horse is injected intradermally into the chest, abdomen or forearm, where a uniform scarlet fever rash not more than 70 hours old is available. A blanching 10 mm. to 40 mm. in diameter appears 4 to 10 hours later, and persists from 12 to 72 hours in most patients suffering from scarlet fever. The antitoxin may be used undiluted or diluted 1 in 10 in normal saline solution—diluted antitoxin should not be used later than six months after preparation.

Treatment

Scarlet Fever Antitoxin. Scarlet fever antitoxin is prepared by immunising horses with a toxin obtained by growing the scarlet fever streptococcus (*Streptococcus scarlatinæ*). There is no standard for this antitoxin and no unit. It is tested in two ways. The toxin when injected into the skin of susceptible human beings causes a skin reaction, and this reaction can be prevented by mixing the toxin with antitoxin before injection; the potency of samples of antitoxin can therefore be tested by seeing whether a given small volume of antitoxin can prevent the skin reaction caused by a certain amount of toxin. The second method of testing depends on the protective power of the antitoxin in rabbits. When 0·25 ml. of a satisfactory sample of antitoxin is injected into the vein of a rabbit, the injection will protect it against the subsequent injection of 6 ml. of a virulent culture containing the living scarlet fever streptococcus.

Therapeutic results of concentrated scarlet fever antitoxin.—G. F. Dick and G. H. Dick, *J. Amer. med. Ass.*, ii/1925, 1693. Treatment of scarlet fever.—A. Joe, *Brit. med. J.*, i/1935, 483.

Reports of paralysis after anti-scarlatinal serum.—*Brit. med. J.*, i/1934, 437.

Immunisation

Dick Test Toxin is injected into the skin of human beings to discover whether they are susceptible or immune to scarlet fever. If they have no circulating antitoxin in their blood, the toxin causes an inflammatory skin reaction. The Dick Test Toxin is a dilution (1 in 1000) of a sterile filtrate from a broth culture of *Streptococcus scarlatinæ*. There is no official standard.

Dick Test Technique. This resembles the Schick test, and consists in injecting intradermally into the left forearm 0·1 ml. of a dilution of the filtrate obtained from a broth culture of *Streptococcus scarlatinæ*. A control of boiled

fluid may be injected into the right forearm in the same manner, but this is not considered necessary. A definite flush about 10 mm. or larger in diameter, coming on in 4 to 12 hours and lasting for 24 to 72 hours, is regarded as a positive reaction.

Sources of error in the Dick test discussed. Alcohol precipitates the toxin and should not be used to sterilise syringe or needles, which should be boiled in distilled water. Observations taken after 24 hours are valueless. The slightest flush or reddening, no matter how faint, constitutes a positive reaction if it measures 10 mm. or more in diameter.—G. F. Dick, *Med. Offr.*, 1933, Feb. 23, p. 75. See papers by G. F. and G. H. Dick, *J. Amer. med. Ass.*, i/1924, 301, 264; *Brit. med. J.*, i/1924, 389, 482.

A clinical study of the test. "Scarlets" in the first five days of illness yielded a positive percentage of 95.15, whereas from the 31st to the 35th day 4.76% were found positive.—A. Joe, *Lancet*, ii/1925, 1321; see also F. A. E. Silcock, *Lancet*, ii/1925, 1327, and *ibid.*, 1334. The test is of no value for diagnosis of scarlet fever but shows whether or not child is immune to that disease.—*Per Prescriber*, 1926, 65.

Scarlet Fever Prophylactic. This preparation, used to produce immunity to scarlet fever, is merely a diluted form of scarlet fever toxin, like Dick Test toxin. It is measured in terms of "skin test doses," a skin test dose being about one-sixth of the amount of toxin ordinarily used in the Dick Test.

The method of immunisation recommended by the Scarlet Fever Committee (U.S.A.) requires 5 doses of 500, 1500, 5000, 15,000 and 20,000 skin test doses of toxin as minimum respectively, with interval of one week between doses. Aetiology, prevention by immunisation, and antitoxin treatment.—W. H. Park, *J. Amer. med. Ass.*, ii/1925, 1180.

Active immunisation with graded doses of streptococcus toxin (scarlatina) will effectively protect majority of susceptible persons. To obtain lasting immunity at least 80,000 to 100,000 skin test doses must be given in 5 weekly injections: 500, 2000, 5000, 25,000, and 50,000. Systemic reactions occur in 10% of cases.—W. T. Benson and A. L. K. Rankin, *Lancet*, ii/1934, 1351.

Snake Bite. In the preparation of Anti-venene the venom is removed either from the living snake or after killing it. This venom is mostly desiccated over sulphuric acid *in vacuo* and a weighed quantity dissolved in sterile water and injected into the horse. The increase in dose proceeds very gradually: the final dose appears to be about 0.6 g. of venom, equivalent to the entire yield of 20 average-sized snakes. The serum is removed in the customary manner and standardised.

Calmette showed that the venom of all snakes is of a similar nature, and obtained his remedy by the inoculation of horses with the poison of the cobra di capello; his serum possesses a strength of 1 in 20,000; that is to say $\frac{1}{10}$ ml. subcutaneously injected into a hare of two kilos in weight suffices to protect it from snake poison which kills a similar hare in eight hours.

It is said that anti-venomous sera are specific even between the venoms of a species of the same genus.

Calmette described the hæmolysins of snake poison; in addition to these bodies snake poison contains neurotoxins, which act on the nervous system, and cytolytins dissolving other tissue elements.

Dose.—Anti-venene is supplied in tubes of 10 ml. This amount, or as much as 40 ml., should be injected. The serum should be as fresh as possible. The injection made within an hour in man; death seldom occurs from serpent poison under 3 hours.

A ligature must be bound above the bite if possible. The wound should be opened up and washed with chromic acid or gold chloride 1% solution.

Difficulty of obtaining sufficient venom—200 rattlers required to secure 60 ml. venom. A preparation from blood rendered immune to mixed poison of S. American vipers and called "Vital Brazil polyvalent Anti-Bothrops" proved as efficient as Calmette's serum.—*Lancet*, i/1927, 244.

Some peculiarities of Australian snake venom.—C. H. Kellaway, *Brit. med. J.*, 1/1933, 1006.

In England adder bites were successfully treated with anti-venene in the summer of 1929.

Liq. Strychninæ, 20 m. hypodermically, of value in snake-bite.—J. M. C. Gray, *Brit. med. J.*, ii/1929, 600.

In the British Isles it may generally be assumed that any bite from an indigenous snake is that of an adder. As the minimum lethal dose of adder venom for an adult is probably 50 mg. and the amount injected by a British adder is between 5 and 10 mg., the results are seldom grave, but in the case of small children and invalids energetic measures are called for: *immediate* tourniquet above fang punctures, suck punctures, then make criss-cross incisions and continue sucking to encourage bleeding, rub crystals of potassium permanganate into the cut and give 10 to 20 ml. antivenin serum (Pasteur Institute), intravenously or intramuscularly.—B. Barnett, *Lancet*, ii/1934, 60.

For the therapeutic use of snake venom see Vol. 1, 964; also this volume, p. 530.

Sporotrichosis (due to *Sporotrichon beurmanni*).—The fungus produces glistening subcutaneous tumours which may ulcerate. In all granulomata which cannot be clearly attributed to the ordinary causes of such lesions the possibility of sporotrichosis should be kept in view. Has been treated by liberal doses of potassium iodide, e.g., 80 grains per diem. Locally, iodine in the form of Gram's solution is useful. The iodine appears to act indirectly by stimulating absorption.

Sporotrichosis of the eyes, a number of cases. Sporothrix isolated from the pus from broken down nodules.—*Oph.*, 1911.

Beurmann states that there are several sporotrichoses according to nature of the numerous parasites cited. That due to *S. beurmanni* is the most frequently met with. It has been found in many localities. Description of the parasite, parasitology, ætiology, pathogenesis and diagnosis.—*Brit. med. J.*, ii/1912, 290.

Sprue or Tropical Aphthæ, *syn.* Psilosis linguæ, Indian Hill Diarrhœa, Ceylon Sore Mouth. Features are sore tongue, stomatitis, and a peculiar form of diarrhœa, due to varieties of bacteria.

Ætiology. Specific cause not yet discovered. Theories of causation and methods of treatment discussed by G. E. Brooke (himself a sufferer).—*J. trop. Med. (Hyg.)*, 1935, 29.

In the endemic areas of the disease there is an excessive protein diet or a diet containing an excess of fat. Excess of proteins stimulates over-production of acids in the gastric juice; the entrance of acid into the duodenum stimulates production of secretin, which leads to over-stimulation of the pancreas and an upset in the balance of other endocrine glands, including the parathyroids, thus causing disturbance of calcium metabolism. The "ionic" calcium of the blood becomes deficient in cases where chronic toxæmia is present, and in the author's opinion this is what occurs in sprue.—H. Harold Scott, *Lancet*, ii/1923, 877.

In eight cases of severe anæmia associated with the sprue syndrome the micro-organism *Monilia psilosis* was isolated.—*Nature, Lond.*, ii/1924, 657.

Ætiology: *Monilia* in tongue scrapings.—Ashford, *Int. Conf. Trop. Amer.*, 1924, 693.

Hydrochloric acid is excreted normally in sprue, which thus differs from pernicious anæmia.—N. Hamilton Fairley and F. P. Mackie, *Indian J. med. Res.*, 1926.

Not a form of pernicious anæmia; Arneth index is normal in sprue instead of being reduced as in pernicious anæmia.—J. D. Tyrer, *Amer. J. trop. Med.*, Nov., 1930.

In Ceylon, an unknown virus affecting the intestinal tract but probably infective with definite incubation period of 3 months or more.—Manson-Bahr and Willoughby, *Quart. J. Med.*, July, 1930.

Treatment. A milk diet is recommended.

Parathyroid, 1/10 grain twice daily, with calcium lactate 10 or 15 grains 3 times daily, gave good results.—H. Harold Scott, *Lancet*, ii/1923, 876; *Brit. med. J.*, ii/1924, 308; and V. Coates, *ibid.*, 623; C. F. Shelton, *Brit. med. J.*, ii/1925, 844.

For further references to this treatment see Vol. I, p. 986.

Monilia psilosis vaccines of value. When used in addition to diet, the outstanding symptoms of sprue have disappeared in two-thirds the time required by diet alone.—*J. Amer. med. Ass.*, ii/1925, 849.

Liver diet, as used in pernicious anæmia, good. In Ceylon, liver soup is an old native remedy for sprue and it has long been recommended in the London School of Tropical Medicine.—*J. Amer. med. Ass.*, ii/1928, 1039.

Tropical sprue and its modern treatment.—N. H. Fairley, *Brit. med. J.*, ii/1934, 1192.

Staphylococci

S. pyogenes aureus. A spherical coccus about 0.9μ in diameter, growing irregularly in clusters or masses. It is gram-positive and grows rapidly in all ordinary media at room temperature, though much more rapidly at body temperature. On agar a stroke culture is at first yellow, and then bright orange. It liquefies gelatin.

S. pyogenes albus. Similar to the above, but cultures are white. It has not been found possible to change one organism into the other.

S. pyogenes citreus. Less frequently met with and differs in colour of cultures, these being lemon-yellow. It is usually far less virulent than the two above.

S. cereus albus and *S. cereus flavus* are wax-like on gelatin. Growth does not liquefy gelatin.—Muir and Ritchie.

Of all non-sporing bacteria staphylococci are the most resistant to desiccation, heat and germicides.—Stitt.

Staphylococcus Antitoxin

Standard and Unit. An International Standard has been adopted, and the unit is defined as the activity present in a given weight of that standard. The antitoxin must comply with the regulations (S.R. & O. 1935, No. 580) made under the Therapeutic Substances Act, 1925. A standard preparation is issued by the National Institute for Medical Research and the unit is the quantity of the standard preparation equivalent to the international unit. There are various methods of comparison in all of which a test toxin is first prepared and the test dose determined by finding the amount of the toxin just sufficient to produce a given effect when mixed with 1 unit, or with a simple fraction of 1 unit of standard antitoxin. Unknown samples of antitoxin are assayed by making mixtures with the test dose of the test toxin and testing these as before. The tests applied are: (1) the power of the toxin to hæmolyse the corpuscles of the rabbit; well washed corpuscles are added to the toxin-antitoxin mixtures; according as the mixture contains excess or insufficient antitoxin, there is no hæmolysis or complete hæmolysis; (2) the power of the toxin to cause skin reactions in guinea-pigs; (3) the power of the toxin to kill mice after (a) intravenous, or (b) intraperitoneal injection.

Staphylococcus Toxoid. Staphylococcus toxin of high potency obtained from selected strains of staphylococci is treated with formaldehyde sufficient to give from 0·1% to 0·15% w/w of H·CHO and incubated at 37° for 14 days. Exceedingly useful in treatment of severe cases of various localised staphylococcal infections, including recurrent furunculosis, chronic and subacute osteomyelitis, acne vulgaris and patients convalescing from acute staphylococcal toxæmia.—C. E. Dolman, *Lancet*, i/1935, 307; see also *J. Amer. med. Ass.*, i/1933, 100; *ibid.*, i/1934, 1699, and *J. infect. Dis.*, 1934, 172.

Standard. Staphylococcus toxoid must comply with the tests to ensure reduction of toxicity, and with tests for non-specific toxicity and for potency as an immunising antigen, prescribed by the regulations (S.R. & O. 1935 No. 580) made under the Therapeutic Substances Act, 1925.

Estimation of circulating staphylococcus antitoxin only of diagnostic value in bone infections in which there is doubt as to causative organism. Amount of circulating antitoxin readily increased by injections of staphylococcus toxoid and this is attended with clinical improvement in the majority of cases of furunculosis treated, but acne does not respond as well as do pure staphylococcal infections. Very few severe reactions from injections observed. Six doses 0·05, 0·1, 0·2, 0·4, 0·5 and 0·6 ml., at weekly intervals given intramuscularly.—D. S. Murray, *Rep. to Therapeutic Trials Committee, Lancet*, i/1935, 303.

Anti-staphylococcus Serum. For some years a combined antitoxic and "anti-bacterial" serum was prepared at the Lister Institute, but little is known of its clinical value. The latest method of production has been the immunisation of a horse by means of a specially prepared staphylococcus toxin, the natural serum then being drawn off. A concentrated preparation which consists of the pseudo-globulin fraction of the serum has been used by Panton and colleagues (Panton, *Lancet*, ii/1931, 1187; *ibid.*, i/1932, 506; *ibid.*, ii/1932, 1019). It is reported that the antitoxin is chiefly of value in pyæmic cases.

Streptococci

Streptococcus pyogenes. Occurs in chains, the cocci being slightly larger than staphylococci (1 μ in diameter). The distinction, *Str. longus* and *Str. brevis*, has been made as referring to the length of chains. Involution forms are seen in cultures, some of the cocci being as much as double size. The organism is gram-positive. It grows more slowly than the staphylococcus and dies out more readily. It ferments lactose, saccharose and salicin, and usually has a strong hæmolytic action (on blood agar). In broth, the species producing the longest chains grow most distinctly in form of spherical granules—producing short chains giving rise to a finer deposit. The name, *Str. conglomeratus*, is given to the variety forming distinct spherules of minute size.

A streptococcus does not necessarily explain an infection. Virulent forms tend to appear in long chains. Hæmolysis and action on carbohydrates of great value in differentiation.—Stitt.

Varieties. Previously, *Str. erysipelatis* was regarded as distinct from *Str. pyogenes*. This is no longer held. Some have divided streptococci according to length of chains and pathogenicity, but pathogenicity and morphology cannot be taken as a means of differentiation. Growth conditions, hæmolytic and ferment activity, and solubility or insolubility in bile salts, have to be taken into account in addition.

Fermentation. Mervyn Gordon introduced nine tests. (1) Clotting of milk; (2) Reduction of neutral red; (3) to (9) Fermentation, with acid production, of saccharose, lactose, raffinose, inulin, salicin, coniferin and mannite. By means of these Andrewes and Horder defined six varieties, five of which occur in the human being: (a) *Str. mitis* in saliva and fæces as a saprophyte; (b) *Str. pyogenes* as above described; (c) *Str. salivarius*, corresponding to *Str.*

brevis of the mouth. As regards fermentation, this seems to bear the same relation to the next variety as *Str. mitis* to *Str. pyogenes*. It ferments saccharose, lactose, raffinose, sometimes the glycosides, rarely inulin. It clots milk and reduces neutral red; (d) *Str. anginosus*, equivalent to the so called *Str. scarlatinæ* and *Str. conglomeratus*. It ferments saccharose, lactose, sometimes raffinose, reduces neutral red, is actively hæmolytic; clots milk usually and does not grow on gelatin at 20°; (e) *Str. fæcalis*, a short-chained form abounding in the intestine. Ferments actively and reacts to all the Gordon tests except raffinose and inulin. It forms H₂S and does not hæmolyse blood; (f) *Str. equinus*, common in the air and dust and appears to be derived from horse-dung.

The chief features of the three most important pathogenic streptococci are, according to Gordon:—

			Neutral Red	Raffinose	Mannite
<i>Str. pyogenes</i>	—	—	?
<i>Str. salivarius</i>	+	+	—
<i>Str. fæcalis</i>	+	—	+

Hæmolysis. The medium used by Schotmüller is two parts human blood (or rabbit) and five parts melted agar, but 5% to 10% of blood is better. *Most of the streptococci from lesions in the human subject* have hæmolytic action, but occasionally streptococci without the property are found—even in severe cases.

The technique employed by Andrewes and Christie is described by them as follows: Blood-agar plate is not wholly satisfactory for showing hæmolysis, as there are many degrees of hæmolysis; the slighter degrees forming only a narrow zone round the colonies (α -hæmolysis) are distinguished from the wide and conspicuous bands of clearing (β -hæmolysis) seen round the colonies of *Str. pyogenes*. Kind of blood used influences intensity of hæmolysis—horses' blood probably best and rabbits' blood worst of those commonly used.

Hæmolytic powers of *Str. pyogenes* depend upon production in the medium of a toxin (hæmotoxin) capable of disintegrating the limiting membrane of the erythrocytes. *Str. fæcalis* (enterococcus of continental writers) under anaerobic (rarely under aerobic) conditions may produce hæmolysis of blood agar similar to that produced by *Str. pyogenes*. Ordinary peptone broth containing 10% horse serum of pH 7·13, incubated at 37° for 24 hours (or 48 hours for weakly growing strain) is centrifuged till apparently clear. One drop of dense suspension of horse erythrocytes (well washed in normal saline) is added to each 10 ml. tube of broth—the fluid should be opaque and bright red on gently shaking. Incubate at 37° and examine after 20, 30 and 60 minutes and then every hour.

Sir Frederick W. Andrewes points out (*Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 169, 1932) that there is no scientific justification for use of term "*Streptococcus hæmolyticus*," because there are streptococci other than *Str. pyogenes* which hæmolyse blood corpuscles under certain conditions, and there is every degree of hæmolysis. The true *Str. pyogenes* of Rosenbach causes β -hæmolysis in the blood agar plate; it ferments lactose, saccharose and salicin. Any one of these fermentative powers may be absent, usually temporarily, and extra powers may be present, *e.g.*, that of fermenting mannite and even starch. Litmus milk is always rendered acid and sometimes clotted; the latter is really a question of degree and the suggestion made by Horder and Andrewes (1906) to use it as a character for separating certain forms under the name *Str. anginosus* has no sufficient warranty. Even the reduction of neutral red may occasionally be found. Andrewes and Christie consider it doubtful if the capsule exhibited by "*Str. epidemicus*," described by D. J. Davis in 1912, is sufficient to mark it off as a distinct species. This coccus has been found in certain outbreaks of septic sore throat traced to milk from infected cows. It is strongly hæmolytic; its sugar reactions are those of *Str. pyogenes* and in other respects it seems to resemble that organism.

See also *Septicæmia, Vaccine Chapter, Vol. I. p. 920.*

Neutral Red Egg Medium for cultivation of Staphylococci, see **Culture Media.**

Syphilis. *Spironema pallidum*, syn. *Spirochæta pallida*, *Treponema pallidum*.

Spironema Pallidum.

The *Sp. pallidum* varies from 4 to 15 μ in length, averaging 8 to 9 μ . It is much more attenuated than the majority of spirochætes, having a maximum thickness of 0.3 μ , has from 3 to 20, usually from 6 to 8, twists, forming a close, regular and narrow spiral; is actively motile and possesses a single delicate flagellum at each end. Its movements are characteristic and best seen under the dark ground; they consist of a rapid rotation round the longitudinal axis, bending or flexions of the spiral, and a slow forward or backward movement.

The syphilitic virus does not pass through a Berkefeld filter but, given time, cultured spirochætes can grow through. It is readily destroyed by heat at 52°, by drying, and by antiseptics.—Hewlett and McIntosh.

Life Cycle of the Organism. McDonagh in 1912 suggested that the *Sp. pallidum* is merely one stage in the complicated life cycle of a protozoon which he suggested should be called *Leucocytozoon syphilidis*. (See 19th Edn., Vol. II, p. 575.)

The work of Levaditi and associates at the Pasteur Institute, Paris, appears to show that the organism responsible for syphilis passes through a developmental cycle of which *Sp. pallidum* is only one phase.—*Prescriber*, 1934, 255.

The organism of syphilis is not a filter-passer. The rarity with which *Sp. pallidum* is seen in glands and organs in experimental syphilis is said to be because the organism multiplies and diminishes in numbers in cycles, and when it is not seen the number has been reduced beyond that at which they can be found in sections. In the brains of paralytics *Sp. pallidum* is often found in small numbers or not at all, and the forms described by Levaditi as stages in the life cycle of *Sp. pallidum* are not seen.—F. Jahnelt, R. Prigge and M. Rothermundt, quoted by L. W. Harrison. *Med. Ann.*, 1934, 461.

Noguchi's discovery of the spirilla in the cortex cerebri of general paralysis.—*Brit. med. J.*, i/1913, 464; ii/1913, 44.

Sp. pallidum has been transmitted from the brain of general paralytics to the rabbit by prolonged course of injections. Symptoms similar to those of general paralysis in man have been produced and the blood gave a positive Wassermann reaction.—*Brit. med. J.*, ii/1913, 1100.

Cultivation. Serum water, to which a piece of sterile rabbit tissue (preferably kidney or testicle) has been added, is inoculated from the artificially infected testicular tissue of the rabbit (not from human lesions). The serum (in test tubes) is rendered suitable for anaerobic cultivation by a layer of paraffin oil poured upon its surface. After the first cultivation strict anaerobiosis is not essential—the organism can be subcultured on to solid media such as gelatin or agar. The first growths are usually contaminated by other bacteria. Two methods are suggested for separating these from the spirochætes: (1) To grow the spirochætes through filters which retard the passage of other organisms or (2) a method depending on the fact that in stab cultures the spirochætes grow away from the line of puncture into the surrounding medium, while other bacteria fail to do so. Noguchi states that spirochætes cultivated by these

methods are pathogenic in so far that after inoculation into the rabbit's testicle they produce characteristic histological changes and are found growing freely in the infected tissue.—H. Noguchi, *J. Amer. med. Ass.*, July 8, 1911, per *Lancet*, ii/1911, 536. *Brit. med. J. Epit.*, ii/1911, 48.

Directions for Taking Specimens from a Chancre.—*Sp. pallidum* are most abundant in the *margin* and in the *deeper* layers of the base of a chancre. The specimen should contain a minimum of blood cells.—C. H. Mills, *Lancet*, ii/1916, 952.

STAINING METHODS

Giemsa's Stain. The following data are from Muir and Ritchie's *Manual of Bacteriology*, 8th Edn., 1927, p. 118.

Giemsa believes that the reddish-blue hue characteristic of the Romanowsky stain is due to the formation of methyl-azure, and he has prepared this by a method of his own under the name azur I. From this, by the addition of an equal part of medicinal methylene blue, he prepares what he calls azur II, and from this again, by the addition of eosin, he prepares azur II-eosin. The formula for the finished stain is as follows:—

Azur II-eosin 3 g., azur II 0·8 g., glycerin 250 ml., methyl alcohol 250 ml.

For spirochætes the following are Giemsa's directions:—

1. Fix films in absolute alcohol for 15 to 20 minutes. Dry with filter paper.
2. Dilute stain with distilled water—1 or 2 drops of stain to 1 ml. water (the mixture being well shaken). (Sometimes the water is made alkaline by the addition of 1 drop of 1% potassium carbonate to 10 ml. of water.)
3. Stain for 15 minutes (a longer period is often desirable, even 12 or 24 hours).
4. Wash in brisk stream of distilled water.
5. Drain with filter paper, dry and mount.

The method of procedure develops into either a long or rapid method:—

(1) *The ordinary or long method* consists in staining for 12 hours with 1 : 10 or 1 : 15 dilution.

(2) *The rapid method.* The same dilution is used but the slide with stain above is held over a Bunsen burner until steam rises. The process is repeated 3 or 4 times, the final application lasting 2 minutes.

The *long* method is recommended by the Medical Research Committee, Report No. 19, issued 1918.

The method for the preparation of azur 1 is kept secret, but in the 17th Edition, page 512, is described a process for polychroming methylene blue, by treatment with ammonia, to give a methylene azure with similar uses.

Polychrome methylene blue may be prepared by heating 100 ml. of 1% methylene blue solution with 20 to 30 mg. of sodium peroxide for 15 minutes at 100°, and subsequently neutralising with hydrochloric acid.—*J. chem. Soc. Abstr.*, i/1925, 597.

According to W. H. Martindale medicinal methylene blue and eosin will produce a suitable stain, the most satisfactory formula being: Eosin 0·4 g., methylene blue medicinal 0·3 g., glycerin 50 ml., methyl alcohol, acetone-free (not exceeding 0·3%), 50 ml.

This solution was found to give good results with spirochætes.

Azur II in the *U.S. IX* was described as a mixture of equal parts of the chlorides of methylene blue and methylene azur (methylene blue sulphonate).

Long and diligent search is necessary in looking for spirochætes stained by this method. It imparts to the spirochæte a distinctly reddish-violet tinge, similar to that of the neighbouring leucocyte nuclei (the Romanowsky chromatin stain), whilst the bacteria come out blue.

Indian Ink Method (Burri). The method is known in Germany as Tusche Verfahren.

The method requires no special apparatus. A platinum loopful of secretion from a sore is placed on a slide and mixed with an equal quantity of distilled water and an emulsion of Indian ink. The whole is mixed and spread on the slide like a blood film, allowed to dry and examined with oil immersion lens. The ink produces a dark background and the objects stand out white. It is easy to differentiate the two forms of spirochætes.

Good scheme of examination for treponemes (using Indian ink and dark ground illumination, also for gonococci using methylene blue).—E. T. Burke, *Practitioner*, ii/1920, 55.

Permanent staining of spirochætes.—*Annual Report of the Committee of the Privy Council for Medical Research*, 1922-3.

The Indian ink method affords no information regarding the structure of the organisms apart from the arrangement of the spiral turns and shape and size of body. The Giemsa (using wet fixed films) is best.—Wenyon, p. 1334.

Collargol solution 1 in 20 (store in amber bottle) preferable to Indian ink. One drop with one drop of the suspected secretion to be mixed together and allowed to dry on the slide, and then spread with another slide to make thin film. The preparation is examined with 1/12 inch oil immersion lens—the background is perfectly homogeneous.—L. W. Harrison, *Brit. med. J.* ii/1912, 1547.

Or proceed as follows: Make a thin film, fix by radiant heat. Pour the collargol solution over film, decant quickly and stand up to dry in air or incubator. Examine with 1/12 inch immersion lens.—Wyatt Wingrave.

Silver Method (Tribondeau). Use material from infiltrated tissue around chancre, not from surface. Eliminate hæmoglobin, etc., as far as possible by washing (*vide infra*). The *fixative* used consists of a solution of formaldehyde 2 g., acetic acid (pure) 1 g., water 100 ml. The *mordant* is 5% tannin in water. The silver stain is silver nitrate 1 g. in water 20 ml. To 15 ml. of this add ammonia drop by drop until precipitate redissolves; then add the remaining 5 ml. of silver nitrate solution until the solution remains slightly opaque after shaking.

Technique. Dry smear at 37°. Fix by washing with fixative 1 minute and complete by a few drops of absolute alcohol, allowing same to dry on the inclined slide. Add the mordant and warm over flame till just steaming for 30 seconds. Wash, pour off excess and without drying employ the silver stain over a flame for 30 seconds. Wash and dry. *Sp. refringens* and *balanitidis* are darker and distinguished by their morphological character.—*British med. J. Epit.*, i/1913, 16. See also *Rep. med. Res. Com.*, No. 19, 1918. The method is very similar to Van Ermengem's process for flagella—one cannot be certain of getting results every time.—W. D'Este Emery, *Practitioner*, i/1913.

Fontana's Silver Impregnation Method

(a) *Fixing fluid*: Acetic acid 1 ml., solution of formaldehyde 20 ml., water 100 ml.

(b) *Mordant*: 5% tannin in a 1% aqueous phenol solution.

(c) *Silver Solution*: Silver nitrate 0.25% in distilled water. In use, a minute quantity of ammonia is added until there is a distinct *turbidity* (avoid excess).

Dried films (not fixed by heat) are fixed in (a) 1 minute, the fluid being dropped on and renewed once or twice. The preparation is then washed thoroughly, solution (b) is dropped on the film, heated until steam rises and allowed to remain about $\frac{1}{2}$ minute. Again wash in water, drop on solution (c) and heat as before and allow to remain about $\frac{1}{2}$ minute. Finally wash and dry. Spirochætes are dark brown or black, and are easily found. This is a good method.—Muir and Ritchie. It is almost identical with the preceding.

Congo Red. Stained films acidified with dilute hydrochloric acid as reliable staining for bacteria and spirochætes.

A small drop of 2% aqueous congo red solution is placed on the slide and a very small quantity of the bacterial culture or of the exudate to be examined is mixed with it. The drop is then spread out into a tolerably thick film. Allow to dry and wash the slide with 1% hydrochloric acid in absolute alcohol and dry in the air, or films may be spread and stained afterwards and treated with acid. Examine with oil immersion lens. The background will appear as a rule uniform. Bacteria vary somewhat in relation to the dye. Mostly they are clear, sharp and quite transparent, but some will take up the dye and appear as ill-defined bluish-black bodies—this is seen chiefly in old cultures of gram-negative organisms.—T. H. C. Benians, *Brit. med. J.*, ii/1916, 722.

Gentian Violet. The stain is prepared on the lines of Gram's aniline-violet for bacteria:—

Shake 3 ml. aniline oil with 20 ml. of distilled water for 5 or 10 minutes and to the filtered liquid add half its volume of a concentrated alcoholic solution of gentian violet. Fix smears by holding over 1% osmic acid solution for 1 to 2 minutes. Pour the stain over the specimen and heat 20 to 30 seconds over a flame. Wash off with water, dry and examine with oil immersion lens. Spirochætes appear reddish-blue against a rose-coloured ground, *Sp. refringens* being stained more deeply.—*Lancet*, i/1911, 321.

A simple method of staining spirochætes. Suspected material spread on cover slides and fixed by 2% solution of formaldehyde, containing 1% acetic acid, for 2 to 4 minutes. Wash with alcohol 95% and treat with saturated aqueous solution of picric acid. After 10 minutes wash in running water and stain with carbol gentian violet or Ziehl's fuchsin solution, when treponema are stained either violet or red, according to stain. Fuchsin gives more permanent stain, but violet coloration renders organisms more distinctive.—E. Renaux, *Chem. & Drugg.*, ii/1923, 435.

Lead Subacetate. Fix with osmic acid as above, wash in water and cover for 10 seconds with a solution consisting of Liquor Plumbi Subacetatis 1, water to 100. Again wash and cover 10 seconds with a 10% aqueous sodium sulphide solution. Wash and repeat whole process twice. Apply osmic acid solution 30 seconds, wash and dry. Spirochætes, cell debris and bacteria appear black.—A. A. W. Ghoreyeb, *J. Amer. med. Ass.*, May 7, 1910, per *Lancet*, i/1911, 32.

EXAMINATION OF UNSTAINED SPECIMENS

Dark-ground Illumination Ultramicroscope. Employed for demonstrating in a rapid, easy and certain manner the presence of the living organism. Useful to examine a scraping when it is necessary to give an opinion on a doubtful primary or secondary syphilitic lesion. Syphilis cannot, of course, be excluded because the organism cannot be detected on one examination.

The ultramicroscope is a paraboloidal immersion-condenser. The rays of light used are deflected so that they converge obliquely on the object examined, which appears as a bright refractive body on a dark background. Transparent objects otherwise invisible are then easily seen.

Sp. pallidum seen thus is an extremely fine silvery spiral. If so focussed that only the summits of the spirals are illuminated the organism looks like a series of bright dots, not unlike a chain of streptococci. It preserves its spiral form during rest.

The technique of dark ground illumination is ably dealt with by J. Edwin Barnard, Pres. Roy. Microscopical Socy., in *Rep. med. Res. Com.*, No. 19, 1918.

Sp. pallidum. Method of demonstrating, using dark-ground illumination without oil. An ordinary achromatic condenser used dry with Travis' expanding stop replaces.—A. C. Coles, *Brit. med. J.*, ii/1915, 777.

Sp. buccalis, *Sp. refringens*, *Sp. balanitidis* are much larger with wider and more open spirals. *Sp. refringens* has only 3 to 5 turns and is usually blunt at either or both ends. The only spirochætes very like the specific organism are: (1) *Sp. dentium*, found in carious teeth, which is shorter (5 to 10 μ) and coarser, 5 to 15 spirals, the wave length the same as *Sp. pallidum*, but depth of wave is considerably less; (2) *Sp. pertenuis* Castellani (yaws); (3) *Sp. pseudopallida* Loewenthal (ulcerated cancers). In the last two the spirals are not quite so deep or regular, and in the case of *Spirochæta pertenuis* the ends are often twisted into rings or loops.

Sp. pallidum is found below the surface in the lymph only and should be sought at the margin of the lesion. It cannot be detected in the centre of an ulcerated or necrosed area where the saprophytic spirochætes may be seen in large numbers. The organism is found in the largest numbers in mucous plaques, is constantly present in varying numbers in primary untreated chancres, and is usually detected in the papular syphilide and in scrapings from a recently removed enlarged syphilitic lymphatic gland.

The margin of the chancre, papules, or mucous plaque should be gently scraped till blood just begins to exude. The surface is now dried with a swab of plain sterile gauze, and then a little blood or serum expressed by decompression or by bandage. A small drop of this is removed with a platinum needle and mixed with a drop of distilled water on a thin glass slide. A thin cover-glass is now pressed down firmly, so that only a thin layer of fluid remains between the slide and cover-glass. A drop of immersion oil is placed below the slide and on the cover-glass. The condenser must first be accurately centred. This can easily be done with a low objective (1 in. or $\frac{2}{3}$ in.) by means of concentric rings scratched on the surface of the condenser.

Any artificial light can be used. Concentrate the light on the centre of the microscope mirror. After the slide has been placed in position so that there is a layer of oil between the ultramicroscope and the under surface of slide, and after the object is focussed, the ultramicroscope must be racked up or

down and the mirror adjusted till bright illumination with dark background is obtained.

General or local treatment has a marked effect on the number of treponemata found, and the organisms tend to disappear after a few weeks from the site of the primary inoculation, even without treatment. Antiseptics must not have been previously applied to the sore.

Comparison with other Spirochætes. *Sp. refringens* under dark-ground illumination is seen to shoot rapidly backwards and forwards in a straight line and when not rotating so actively is often seen to squirm its way by corkscrew movements, pushing blood corpuscles, bacilli, etc., aside. Serum obtained by swabbing is preferable for examination to scrapings. Stitt says: "While the rotary movement of *Sp. pallidum* is rapid, it does not move across the field with the speed of other spirochætes. Thus *Sp. refringens*, commonly present in genital ulcerations, quickly traverses the field and shows more widely separated spirals. The *pallidum* shows a continuity of its spirals while in motion, but when at rest often shows the appearance of a series of silvery dots or dashes. Many individuals show a bend in the long axis."

In staining with *Giemsa's stain* (diluted 1 in 8) at least 12 hours is best. In the *Indian ink* method at least twice the volume of Indian ink to the drop of serum. Spirochætes are more constantly present in condylomata and mucous patches and far less constantly present in papular secondary skin eruptions than in primary sores. *Dark-ground illumination* is the best method.—*Brit. med. J.* ii/1911, 1283.

Noguchi's Method of Diagnosis of Syphilis.—(*Distinguish from the Noguchi modified Wassermann.*) Boil two parts of the cerebrospinal fluid with 5 parts of a 10% solution of butyric acid in normal saline for a few seconds then add one part of normal sodium hydroxide and again boil briefly. A flocculent or granular precipitate is obtained on standing (in parasymphilitic affections due to presence of a globulin. The test distinguishes general paralysis from other forms of insanity not associated with meningo-encephalitis.

Examination of Dried Serum.—The blood is collected in the usual way in a bent Wright's Tube, and allowed to coagulate. A definite quantity of the serum is pipetted off and allowed to dry on blotting paper. This can then be treated with normal saline and made up to its original volume for conducting the test.

WASSERMANN REACTION.

Complement-Deviation Reaction for the Diagnosis of Syphilis (Wassermann, Neisser and Bruck).

The reaction was elaborated by Wassermann on the principle of the Bordet-Gengou reaction (1901). The Bordet-Gengou reaction is that which occurs when antigen, specific antibody and complement are exhibited together. As Wassermann was not able to use a culture of the *Sp. pallidum* he made use of an extract of syphilitic *fœtus tissue* rich in spirochætes. Subsequent work showed, however, that the reaction was not a true Bordet-Gengou reaction, was not truly specific, and did not depend on an interaction between the spirochætes and a specific anti-spirochætal antibody, but was due to an altered condition in the serum of a patient during the active stage of infection, whereby on the addition of various lipoidal substances an alteration occurred which caused complement to be interfered with in its activity. Modifications using "antigen" extracted from normal organs are now employed to a large extent. For the reaction are required:

(1) **Antigen**, which is usually an alcoholic extract of normal heart to which some cholesterin has been added.

(2) **A hæmolytic system**, usually anti-sheep, requiring sheeps' red cells and rabbit serum from a rabbit immunised against sheeps' red cells.

(3) **Complement** obtained in guinea-pig serum.

(4) **Serum of patient**, and **controls** of normal and syphilitic sera. The sera should be inactivated by heating for 30 minutes at 55° to 56° before use.

The only reliable test is when the constituents for the reaction have all been derived from separate sources and can be accurately standardised. The so-called rapid clinical methods are valueless.

Washed Sheep Corpuscles are prepared from the fresh blood by removing fibrin by clotting—rapidly stirring at the time of drawing from the animal. Centrifuge with a powerful centrifuge and pipette off the serum. Add normal

saline solution and again centrifuge several times, and finally dilute with normal saline solution making approximately a 10% suspension of the corpuscles.

Methods of carrying out the Wassermann Reaction. The methods of performing the test are legion, but the principles involved are but slightly different from those in connection with the complement fixation test in general. Three agents are involved in the actual reaction, antigen, patient's serum and complement. When these have been allowed to react for a suitable period (1 hour at 37°) or overnight in the icebox, sensitised red cells are added and the mixture incubated for 1 hour at 37°. This determines the presence or absence of hæmolysis, indicating the presence or absence of unabsorbed complement. To establish a positive reaction it must be shown: (a) that the patient's serum alone absorbs no complement, or at the most but a small fraction of it; (b) that the same is true of antigen; (c) that the mixture of serum and antigen absorbs an amount of the complement greatly in excess of the sum of the small amounts absorbed by the individual reagents separately.

There are three variables involved in the reaction—antigen, serum and complement. Quantitative results may be obtained by keeping two of these constant and varying the third.

Topley and Wilson prefer the method whereby the antigen and complement remain constant and the variable third is the patient's serum. The serum is tested with dilutions of 1 : 2.5, 1 : 5, 1 : 10, 1 : 20 and 1 : 40. This gives a direct measure of the concentration of the Wassermann body in the serum under test. The serum control is put up with the largest amount of serum employed in the actual test, and it is necessary to standardise the complement.

NOTATION. With the large number of methods employed there are, of necessity, many notations. Some use + + + +, + + +, + +, +, + -, and - to indicate strongly positive, positive, moderately positive, weakly positive, doubtful, and negative results respectively. Others employ numerals from 0 to 4 to indicate the amount of hæmolysis in the various tubes of the reaction; thus Kolmer uses 4 4 4 4 4 to indicate a strong positive, 4 4 0 0 0 to indicate a moderate positive, and 0 0 0 0 0 to indicate a negative. Nevertheless it is desirable that a brief written note be added such as—"definitely positive," "doubtful" or "definitely negative."

Varying amounts of blood serum are required for the carrying out of the W.R. according to the method employed. 1 ml. of blood or 0.25 ml. of serum is the minimum quantity but 5 to 20 ml. of blood and an ample supply of serum enables the test to be repeated if necessary and confirmed. Generally speaking the blood may easily be obtained by venepuncture or simply by "milking" the finger or lobe of the ear.

For further details of reliable methods of carrying out the Wassermann Reaction see *Spec. Rep. Ser. med. Res. Comm.*, 1921, No. 14.

Interpretation of Results

Interpretation of the Wassermann Reaction in adults.—T. E. Osmond, *Lancet*, ii/1929, 677.

The reaction only of value when interpreted in conjunction with other findings. A single negative of little value in presence of suggestive findings; no evidence of cure.—R. A. Kilduffe, *J. trop. Med. (Hyg.)*, 1923, 118.

The reaction in the child at birth is in close agreement with that of the mother, but during the first few weeks of life the majority of children born with a positive reaction lose that reaction, and not only remain negative to Wassermann, but fail to develop clinical signs of syphilis during first 2 years. A positive reaction in new-born infants is therefore of no diagnostic value, and the incidence of congenital syphilis is much less than serological data indicate. High incidence of syphilis in adults due either to acquired, or, less probably, to late congenital syphilis. Effects of syphilis in mother chiefly seen in later months of pregnancy, leading to premature birth and premature still-birth. The diagnosis of syphilis in the new-born can be made definitely only after careful review of clinical, serological and pathological findings.—J. N. Cruickshank, *Child Life Investigations: Maternal Syphilis, etc.*, *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 82, 1934; *Brit. med. J.*, i/1924, 532.

A positive W.R. in the child at birth cannot be taken as an indication that the child is syphilitic. Over 90% of children born with a positive reaction lose it later.—J. N. Cruickshank, *Lancet*, i/1924, 675.

Unless both mother and child have a positive Wassermann reaction, or both have a negative Wassermann, the mother should not be allowed to suckle the

child direct, but the milk is not contagious and if the mother is diseased the milk may be drawn off into a sterile bottle and fed to the child with impunity.—J. J. Abraham, *Brit. med. J.*, ii/1932, 237.

Doubts as to value of the reaction. Because the Complement Deviation Test may be + it is inaccurate to say the case is syphilis.—A. S. Leyton, *Brit. med. J.*, i/1918, 523.

The test is not so reliable in women as in men. While it can generally be assumed that a positive reaction in a pregnant woman means syphilis, it cannot be assumed that a negative reaction means absence of syphilis or successful treatment, as 30% of congenital syphilitic children are born to mothers with negative Wassermann. If a woman has once had syphilis, as long as she is capable of bearing children, such children may be syphilitic, but if a woman is treated through each pregnancy exactly the same as if she has just acquired the disease her chances of having a healthy baby are almost as good as those of a non-infected woman—except where she has a persistently positive C.S.F. Wassermann in spite of treatment.—J. J. Abraham, *Brit. med. J.*, ii/1932, 239.

Parasyphilitic Conditions in Relation to the Reaction. The W.R. in blood and spinal fluid is often valuable in confirming a diagnosis of early tabes, but as a guide to progress and further treatment it is unreliable, and one frequently finds actively progressing tabes with a history of syphilitic infection despite a negative reaction in both blood and fluid.—C. P. Symonds, *Modern Technique in Treatment*, Vol. II, p. 40.

Routine cerebrospinal fluid examination in diagnosis of nervous diseases. Cell counts, protein content, Wassermann reaction, colloidal gold test.—A. Douglas Bigland, *Lancet*, ii/1920, 687.

CEREBRAL SYPHILIS.—A definitely positive W.R. indicates infection—negative result is not always of value. In tabes, a negative reaction in the blood is by no means uncommon during a quiescent phase; even in the spinal fluid the reaction is sometimes negative. In cerebral syphilis, when the disease is progressive, a +W.R. in the blood can almost always be obtained. In the cerebrospinal fluid the reaction may be + or —.—G. Riddoch, *Lancet*, ii/1923, 103.

According to McDonagh the reaction is positive in 40% of primary cases, 97% of untreated secondary cases, and 70% of tertiary cases.

Noguchi gives the following figures as indicating the percentage of positive W.R. as determined by various serologists: Primary syphilis, 69.8; secondary syphilis, 89.4; tertiary, 78.1; hereditary, 94.5; cerebrospinal, 47.6; general paresis, 88.1; tabes 62.66. With cerebrospinal fluid general paresis gave 90.2, tabes 56.2 and cerebrospinal syphilis 19.

Lange's Colloidal Gold Test, see *Cerebrospinal Fluid Examination*, p. 352.

Influence of Drugs on the Reaction. Potassium iodide and the early arylarsonates (sodium aminarsonate, Atoxyl and Soamin) seem to have little, if any, action on the reaction.

Emery finds that **mercury itself inhibits the reaction.**—*Lancet*, i/1911, 595.

Casoni took 16 individuals, 12 of whom were definitely non-syphilitic, and 4 suffering from syphilis, and observed their reaction to the test before and after giving the following drugs: iron citrate, sodium arsenate, strychnine, guaiacum, sodium glycerophosphate, and quinine. In the twelve non-syphilitic cases the Wassermann reaction was negative both before and after treatment. In the syphilitics one remained unaffected by treatment, the reaction being positive all the time. Of the remaining 3, in one the reaction disappeared completely under arsenic, and in the other 2 it was much less marked. Quinine abolished the reaction entirely in one, while it did not modify it in the others. It was only the quinine and arsenic which modified the reaction, and this not in every case. Iron, strychnine, guaiacol, and glycerophosphate had no effect.—*Brit. med. J. Epitome*, i/1911, 24.

Subcutaneous injection of 1 mg. adrenaline hydrochloride prevents reaction giving rise to a false "positive" W.R.—*Indian J. med. Res.*, July 1925, p. 10. *J. Amer. med. Ass.*, ii/1925, 1432.

General References to the Reaction

B.M.A. (1910) DISCUSSION ON COMPLEMENT DEVIATION METHODS IN DIAGNOSIS; Prof. Wassermann's paper.—*Brit. med. J.*, ii/1910, 323, 1427.

Wassermann's (original) test. For a good description see *Brit. med. J.*, ii/1911, 1504.

Rationale of Wasserman reaction.—J. E. R. McDonagh, *Lancet*, ii/1921, 1319.

Method of procedure for large number of tests.—P. Fildes and J. McIntosh, *Lancet*, ii/1916, 751.

A quick method of performing with small quantities of serum.—F. E. Taylor, *Lancet*, i/1918, 19.

Serological tests for syphilis with very small amounts of patients' serum. Describing how with 0.15 ml. of serum, which is obtainable from as little as 0.5 ml. of blood a Wassermann reaction and three flocculation tests can be carried out.—E. J. Wyler, *Rep. publ. Hlth med. Subj., Lond.*, No. 74, per *Brit. med. J.*, ii/1934, 953.

Chemistry of Wassermann reaction. The bodies responsible for the + syphilis reactions are solely contained in the euglobin group of proteins. The hæmolytic bodies in hæmolytic amboceptor are chiefly contained in the pseudo-globulin group.—*Brit. med. J. Epit.*, ii/1922, 44.

Surface tension due to the alcohol used in making the antigen thought to be the important factor in the Wassermann reaction. The alcohol itself is the antigen.—V. B. Nesfield, *Lancet*, i/1917, 18.

Effect of malaria on the reaction in syphilis. Chronic malaria has no appreciable effect on reaction. Acute malaria has the effect of increasing the anti-complementary powers of this serum. Pyrexia due to non-malarial infection has no effect on reaction.—E. H. R. Altounyan, *Lancet*, i/1924, 73.

Serum diagnosis in Syria—an account of work undertaken to estimate value of serological tests in syphilis, tuberculosis, dysentery, typhoid and typhus. An analysis of 2868 cases.—*ibid.*

OTHER SEROLOGICAL TESTS

Sachs-Georgi Reaction. Mix a 1 in 5 alcoholic extract of heart muscle (beef, human, or guinea-pig), with 2 parts of alcohol, and to 10 ml. of this add 0.45 ml. of 1% cholesterol solution. (The proportions may have to be varied.) Dilute with 5 parts of normal saline solution, taking care that no precipitation occurs and that the dilution does not become cloudy. Inactivate patient's serum by heating for $\frac{1}{2}$ hour in a water-bath at 55° and dilute with 9 parts of normal saline solution. Place 1 ml. of the diluted serum in a test-tube and add 0.5 ml. of the diluted antigen. As antigen control, mix 0.5 ml. of diluted antigen with 1 ml. of normal saline solution (0.85%) and as serum control mix 1 ml. of diluted serum with 0.5 ml. of normal saline solution and alcohol mixed in the proportion of 5 to 1. A known positive and a known negative serum are used for control. Incubate test-tubes for 18 to 20 hours.

Interpret with an agglutinoscope after 18 to 24 hours. The antigen control should be absolutely clear, and if the serum control shows any precipitation repeat the test. Distinct light particles against the dark background indicate positive reaction—negative sera are entirely clear or slightly opalescent. Strongly positive reactions show up within 2 or 3 hours in the incubator and can be read microscopically.

Cerebrospinal fluid should be used undiluted in 1 to 1.5 ml. amounts.—Stitt, p. 250-252.

Results closely approximate data from Wassermann reaction.—W. R. Logan, *Lancet*, i/1921, 14.

Compared with Wassermann tests.—T. Taniguchi and N. Yoshinare, *Brit. med. J.*, ii/1921, 239. See also P. Parthasarathy and co-workers, *Brit. med. J.*, i/1922, 594.

Quicker working and a higher degree of sensitiveness effected by using highly concentrated extracts. The old S.-G.R. now termed the "*Lentocol*," or slow reaction, and the new modification, the "*Citochol*," or quick reaction.—per *Prescriber*, 1929, 275. "*Citochol*" more sensitive than the old S.-G.R. but useless for testing spinal fluid.—*ibid.*

Meinicke's Third Modification of this test uses an alcoholic, non-cholesterolised horse-heart extract for antigen.

Meinicke now uses a larger amount of balsam of tolu, and ox-heart instead of horse-heart muscle; dilutions being made with 3.5% salt solution, containing sodium carbonate, and the reaction is carried out at a temperature of 20°. When positive, the mixture becomes clear—slightly positive, opalescent—negative, turbid.—per *Prescriber*, 1929, 273.

Sigma (Σ) Reaction.—"S.R." (Dreyer and Ward, *Lancet*, i/1921, 956). Instead of five variables there are only two. An antigen which is a mixture of an acetone-free alcohol-soluble heart extract and cholesterin is used. Flocculation after 9 hours at 37° is a + reaction.—A. F. Rook, *Lancet*, i/1922, 118.

It is well worth while to use the Sigma test and the W.R. in conjunction as neither singly gives a true result in every case.—J. Menton, *Practitioner*, ii/1924, 379.

Apparatus for the Sigma reaction.—J. W. Bigger, *Lancet*, ii/1924, 742.

The S.R. perhaps more sensitive than the various modifications of the W.R. It is of high specificity and permits one to follow the results of treatment. Some factors influencing the flocculation methods of Dreyer-Ward and Sachs-Georgi.—I. R. Morch, *Lancet*, ii/1924, 58.

Comparison of Sigma and Wassermann Reactions. The S.R. appears to be of as great diagnostic value as the W.R. The technique of S.R. is simple but reading of results requires greater care and experience. In the study of syphilitics undergoing treatment S.R. is undoubtedly the method of choice. In serum diagnosis of syphilis, both methods should be used in elucidation of difficult cases.—E. H. R. Altounyan, *Lancet*, i/1924, 73.

Sigma reaction results.—P. H. Jones, *Brit. med. J.*, i/1925, 821.

By means of the Sigma reaction it is possible to estimate with a high degree of accuracy the amount of reacting substance in the serum of cases of syphilis, the probable error of any single determination being about 6%, as compared with an average deviation in the case of the Wassermann reaction of 24%.—P. H. Jones, *Brit. med. J.*, i/1925, 821.

Kahn Test. To a 1 in 5 alcoholic beef-heart extract add 4 mg. cholesterol to each ml., a similar amount of extract being retained as a non-cholesterolised antigen control. Dilute the alcoholic antigen with normal saline solution (0.85%) in proportion of 1 to 2, and the cholesterolised antigen in the proportion of 1 to 3. Pipette 1 ml. of alcoholic antigen into a small test-tube, add 2 ml. of salt solution, and mix rapidly. The resultant opalescent mixture is ready for use. Dilute the cholesterolised antigen similarly, using 3 ml. of salt solution; this has a tendency to precipitate, and is best kept in the incubator when not in use. Dilutions should be freshly made and not used until $\frac{1}{2}$ hour after dilution.

Place in each of 2 agglutination tubes 0.3 ml. of undiluted inactivated patient's serum. To the first tube add 0.05 ml. of diluted non-cholesterolised antigen and to the second the same quantity of diluted cholesterolised antigen; agitate vigorously. Strongly positive sera may show definite precipitation, particularly with the cholesterolised antigen. To bring out precipitation in weaker sera place test-tubes overnight in incubator at 37°. Read results next morning as follows:—(1) Precipitation consisting of one or more large clumps is denoted by + + + +; (2) a large flocculent precipitation by + + +; (3) moderate-sized flocculi or granules by + +; (4) small-sized flocculi or granules by +; (5) fine flocculi or granules by \pm ; (6) negative precipitation by —.—Stitt. (Some details have since been altered.)

Comparison of Kahn and Wassermann Reactions. A comparison of the Kahn and Wassermann tests.—T. E. Osmond and D. McClean, *Brit. med. J.*, i/1924, 617.

Wassermann, Sachs-Georgi and Khan tests compared.—*Brit. med. J. Epist.* ii/1924, 16.

Comparison of Kahn reaction with Wassermann test in 29,000 cases showed that the Kahn test gave fewer false reactions and consistently appeared more delicate, especially in early cases and cases following treatment.—*Amer. J. Syph.*, per *J. Amer. med. Ass.*, ii/1925, 65.

A series of 2500 cases clinically free from syphilis gave 2493 negative reactions by Kahn test.—per *J. Amer. med. Ass.*, ii/1925, 1428.

Kahn test gaining in popularity. A more rapid and dependable test than the Wassermann; has replaced the latter in the Michigan Department of Health.—*J. Amer. med. Ass.*, ii/1925, 1733.

Kahn test superior to Wassermann.—*U.S. Nav. med. Bull.*, Nov., 1925, per *J. Amer. med. Ass.*, ii/1925, 1916.

Of 9 tests applied simultaneously to 600 sera the Wassermann was the most deficient in sensitivity (66%), with the Sachs-Georgi next, the best being the Meinicke reactions with a sensitivity of 81.7% to 90.3%. The only complete

specific test was the routine Kahn. Of the 6 tests applied simultaneously to 380 fluids the most sensitive was the Kahn, whilst the Wassermann was much less so. In view of the fact that the Wassermann test on blood is the most difficult, the least sensitive, and not the most specific, one can but deplore that there should be such a desperate clinging to the Wassermann even to-day, especially in public medicine. Even for spinal fluid examinations the Kahn is vastly superior.—J. E. Nicole and E. J. Fitzgerald, *Lancet*, i/1934, 652.

Kline's Microscopic Slide Precipitation Test

Apparatus. Ordinary microscopic slides are washed in soap and water and rinsed, allowed to remain in 95% alcohol for a short time, dried and flamed. Four paraffin rings (with an inside diameter of 11 mm. to 12 mm.) are made on one surface by transferring a small amount of hot paraffin on a stiff wire (gauge 19) wound with thread (or hat wire) bent to the form of a circle.

The pipettes for delivering the sera are 1 ml. pipettes graduated in 0.01 ml. Those for the antigen have the ends drawn out so that each drop of antigen dilution equals 0.015 ml. The diameter of the tip over all is about 1.25 mm.

Vials for preparing the antigen dilution as used by Kahn.

A humidor cover consisting of a wooden lid, 16½ in. by 4 in. by 1½ in. inside diameter, with a moistened blotter fastened in place with thumb tacks.

Antigen. The antigen and antigen dilution are prepared as for the Kahn test. The antigen titration likewise is done as for the Kahn test. The antigen dilution should be made up just before pipetting the sera. Some antigen dilutions have been found to work only within 15 minutes of their preparation.

Sera. Obtained as for the Wassermann test, and heated to 56° for 30 minutes.

The Test. Into each ring 0.06 ml. of the undiluted serum to be tested is delivered from a pipette. It is advisable to work with not more than twelve sera (three slides) at a time. After all the sera are pipetted, 1 drop of Kahn's antigen dilution (0.015 ml.) is allowed to fall into the serum in each ring. After all the antigen is pipetted, the small amount in each ring is evenly distributed by rapidly stirring the mixture with a tooth pick. The slides are then placed below the humidor cover and allowed to remain at room temperature for 10 minutes. The first slide is then removed, rocked for about 60 seconds and read immediately. The readings are made through the microscope (16 mm. objective, 10 or 12.5 eye-piece) with the light cut down as in studying urinary sediments, and recorded in terms of pluses according to the size of the clumps. The test should be done in duplicate, different antigens being used.—B. S. Kline and A. M. Young, *J. Amer. med. Ass.*, i/1926, 929.

The Kline test is of most value as an eliminating test for the exclusion of syphilis and for test of cure rather than for diagnosis.—T. E. Osmond and K. E. Hughes, *Lancet*, i/1931, 130.

Chief value of Kline test is in later stages of syphilis under treatment; in cases, e.g., interstitial keratitis, where it is especially important that syphilis should be excluded; and as a general supplement to Wassermann reaction. It is relatively simple, rapid and inexpensive and only a very small quantity of serum is required. The antigen-emulsion retains its efficiency for a relatively short time only—hence the test is suitable only for use in laboratories where large numbers of sera are examined at one time.—W. V. MacFarlane and J. Gorman, *Brit. med. J.*, i/1935, 469.

Vernes Flocculation Test. Depends on a flocculation reaction between the patient's serum and a special reagent, "Perethynol," prepared from horse-heart muscle by means of ethylene chloride and alcohol. A suspension of the reagent in saline is flocculated in the presence of syphilitic antibody and the degree of hæmolysis ascertained by a special photometer, the results being given quantitatively in definite figures. The only test officially recognised by the Municipality of Paris and the French Government. Individual error almost impossible. More mathematically accurate than either the Wassermann or the Sigma tests.—per *Prescriber*, 1928, 264; see also E. Offenheimer, *Practitioner*, i/1928, 376.

Hinton Test. Consists of an "agglutination" by syphilitic sera of a suspension of cholesterol in glycerinated hypertonic saline containing a trace of the alcohol-soluble, ether-insoluble extractives of beef muscle. An economical, simple, and highly sensitive test, but should be reserved as a supplementary test to the Wassermann.—J. H. Ferguson and E. C. Greenfield, *Brit. med. J.*, i/1929, 494.

General References to Syphilis

For brief details of the Venereal Disease Act, 1917, see Vol. I., p. 1014.

Combating venereal disease in Great Britain.—Col. L. W. Harrison, *Lancet* i/1925, 1216.

Anti-venereal Campaign. In syphilis, the indications are that the Act has been attended by a considerable measure of success. The majority of persons infected with syphilis in this country resort to the treatment centres and the returns from these centres show a maximum of 42,805 in 1920, falling to 21,521 in 1933. Syphilis is not being transmitted so freely as in the past to wives and offspring, the registered mortality rate from syphilis in infants having fallen steadily from the maximum of 2·03 in 1917 to 0·40 per 1000 in 1933. Another effect is evident in the scarcity of cases nowadays showing severe external signs of the disease.—*Rep. med. Offr Minist. Hlth, Lond.*, 1933, 141.

In Paris syphilis is on the increase. The number of cases, which fell regularly from 1920 to 1924, began to rise in 1925 and in 1927 was back to the 1920 figure.—*Lancet*, ii/1928, 826.

The possibility of an infection with syphilis taking place through the performance of a p.m. examination is an established fact and syphilis must now be included among the diseases with which pathologists may become infected.—*per J. Amer. med. Ass.*, ii/1928, 263.

Quéry's Serum. *Dose:* Injection, subcutaneously or intramuscularly of 25 ampoules, one a day for 25 consecutive days, ordinarily it is not necessary to renew the treatment. This preparation is made by immunising monkeys with a "polymorphous bacterium" isolated from a syphilitic affection.

Relief of symptoms.—J. Dobriansky, J. H. Sequeira and T. Thompson *Lancet*, i/1920, 903. Two cases unaffected and 8 cases out of 9 (intramuscular use) improved.—*Brit. med. J.*, ii/1922, 624, 635.

Tetanus. For general information and references to literature see Vol. I., p. 923.

Tetanus Antitoxin. Standard. The international standard is a sample of dried antitoxin kept in the Serum Institute at Copenhagen. The British Standard, which has been very carefully compared with the international standard, is kept in the National Institute for Medical Research, Hampstead.

The Unit. The unit is the specific antitoxic activity present in a fixed weight of the international standard. The British unit is the same as the international unit, but the American unit has twice the amount of activity represented by the international unit.

Method of Standardisation. To estimate unknown samples of antitoxin a test toxin is first prepared. Tetanus toxin, unlike diphtheria toxin, can be prepared as a stable dry powder by growing *Bacillus tetani* in broth in the absence of air; the organisms in the broth are killed and the broth is filtered. When this sterile filtrate is saturated with ammonium sulphate, a precipitate is formed which can be dried and powdered. This can be preserved in sealed ampoules. Mixtures of toxin and the standard antitoxin are first made in order to find the smallest quantity of toxin which when mixed with 0·2 unit of antitoxin and injected under the skin of guinea-pigs or mice, causes death in four days. This dose is called the L† dose. The injected volume is 4 ml. for a guinea-pig or 0·5 ml. for a mouse. The L† dose of the test toxin having been determined, the sample of unknown antitoxin is then mixed in varying amounts with the L† dose of the test toxin and these mixtures are injected into guinea-pigs or mice, in order to find the mixture which kills the injected animals in 4 days. The amount of unknown antitoxin in this mixture contains 0·2 unit.

Tick Fever. Ross and Milne (1904) first showed the so-called African tick fever to be caused by a spirochæte of closely similar character to that of relapsing fever, but bacteriologically it is more convenient to keep the two diseases separate,—associating

tick fever with *Sp. Duttoni*. Dutton and Todd in the Congo Free State, also Greig and Nabarro in Uganda, worked on the subject. Clinically, the fever closely resembles relapsing fever, but the periods of fever are somewhat shorter—rarely lasting more than two or three days. The organisms are much fewer in the blood than in the European relapsing fever. Morphologically they are almost the same.—Stitt.

Sp. Duttoni—the parasite of tick fever. Experimental investigation.—Sir W. B. Leishman, *Lancet*, ii/1920, 1237.

The transmitting agent, *Ornithodoros moubata*, infests rest-houses on the route of travel, hiding in the crevices of floors and walls and feeding at night. The female transmits the spirochæte to its ova. Natives suffer severely in childhood, but develop immunity later.—Stitt.

Through the bite of ticks from Nyasaland, collected in the hut of a native in whose house cases had occurred, Leishman was able to infect a monkey. The spirochætes appeared in the blood of the animal on the sixth day and it died on the thirteenth day. From the monkey, transmission was possible to mice.—*Brit. med. J.*, ii/1908, 1435.

Tick-bite Fever. A mild disease occurring in Southern Africa, with no mortality, no sequelæ and almost no complications: not contagious. Only larval ticks convey the disease, and in most cases the tick is *Amblyomma hebræum* but sometimes it is a rhipicephalus. The incubation period is 8 to 9 days. It is often confused with typhoid, paratyphoid, measles, tick fever and perhaps typhus, but it is a well-defined clinical and pathological entity belonging to the group of typhus-like diseases.

It is clinically similar to typhus, the patient's blood serum agglutinates the proteus strains X19, X2 and X Kingsbury, the patient's blood injected into guinea-pigs produces a fever similar to that caused by typhus blood and which may be transmitted to other guinea-pigs, the brains of such guinea-pigs may show nodules with rickettsia-like bodies and their blood serum agglutinates the proteus strain X Kingsbury. The bite-mark is the most characteristic symptom: when first seen it has usually become a red papule with a discoloured centre, which later becomes necrotic and black and eventually drops out. The regional lymph glands become swollen and painful, and there is usually headache, rash, continuous fever for 10 days, and later hallucination, delirium, photophobia and toxæmia: the fever curve resembles that of typhus.—J. M. Troup and A. Pijper, *Lancet*, ii/1931, 1183.

Trypanosomiasis (Sleeping Sickness). The disease is endemic on the West Coast of Africa, notably in the Congo Basin, and is caused by the entrance into the blood and cerebrospinal fluid of the parasite *Trypanosoma gambiense*. It causes a complete dislocation of the brain functions, slow inflammatory process goes on in the brain cells for years, gradually the individual becomes languid in the extreme, and he has not physical energy to walk, speak, or even feed himself.

The condition known as sleeping sickness may be regarded as the terminal stage of trypanosome infections. The average duration is 4 to 8 months. Mania is not uncommon. Blood or gland-lymph examination, or, if this be negative, hepatic or splenic puncture, should establish diagnosis. General paralysis of the insane, cerebral tumour, and forms of meningitis have features in common.

A study of the pathological lesions found in infected monkeys showed three distinct pathogenic types as follows:

(1) **Chronic manifestations** with few trypanosomes, approaching in 4 to 8 weeks sclerotic and infiltrative lesions of hæmatopoietic organs, meningoencephalitis, sclerosis of the myocardium, and cachectic phenomena predisposing to extraneous complications. This group characterises the pathogenic action of human trypanosomes of the *Glossina palpalis* regions.

(2) **Rapid manifestations** with few trypanosomes, approaching terminal lesions in 2 to 4 weeks, with hyperplastic and hæmorrhagic phenomena in the hæmatopoietic organs, myocarditis, serositis and nephritis, the early passage of parasites into the cerebrospinal fluid, and lesions in the choroid plexuses. This group characterises the pathogenic action of human and animal trypanosomes of the *G. morsitans* and *G. swynnertoni* regions.

(3) **Irregular manifestations** of intermediary type reaching, in 8 to 10 weeks or 8 to 14 months, lesions of the first or second type, and usually chronic lesions associated with rapid terminal lesions. This group characterises the pathogenic action of trypanosomes of animal origin of *G. palpalis* regions (Damba Island).

Trypanosomal myocarditis frequently causes death in inoculated monkeys, due to massive deposits of trypanosomes in the myocardium. In view of the cardiac disturbances and sudden deaths in human infections due to *T. rhodesiense* it is extremely probable that in these forms the cardiac changes are very severe and sometimes more important than the changes in the nervous system.

The cerebrospinal fluid is a defensive mechanism against the invasion of trypanosomes (from the choroid plexuses), until its albuminoid content is raised.—M. Peruzzi, "Final Rept. League of Nations Int. Com. on Human Trypanosomiasis," 1928.

Infection of man by *T. rhodesiense* was first recognised by Stephens and Fantham (1910). It is more serious than that caused by *T. gambiense*, running a course of only a few months and producing only exceptionally the symptoms of sleeping sickness since it is too rapidly fatal. Its distribution is very limited, viz., to the districts east and west of Lake Nyasa and in N. Rhodesia, Nyasaland, the south-east corner of Tanganyika territory, and the north-east part of Mozambika.—Wenyon.

T. Cruzi. First discovered by Chagas in 1907 at Minas in Brazil, and since found to occur in other parts of Brazil and in Venezuela and Peru. Causes a form of trypanosomiasis often termed CHAGAS' DISEASE, occurring in children, but assuming an acute form in the first year of life. There is fever, and anæmia, and enlargement of liver and spleen and lymphatic glands, especially the thyroid. May occur in adults. Reduviid bugs are the transmitting host. The armadillo is a reservoir host.—Wenyon.

Trypanosoma Gambiense, Characters of. The trypanosome of Gambia was first named and described by Dutton, who lost his life in 1905 in West Africa whilst engaged in his work on this disease.

On account of its scarcity in the blood of man, its morphology has been studied chiefly in the blood of animals, e.g., guinea-pig and rat. Its length is between 15 μ and 30 μ . There are various forms—a short and broad which has no flagellum, a long thin form with flagellum, and an intermediate form. The short are the result of division of the long ones and they grow into long forms which divide (Robertson, 1912). Longer forms than above mentioned may be seen up to 40 μ . Macfie (1913) pointed to a stumpy form as a distinct species, *T. nigeriense*—probably merely a strain.

The nucleus is central and the kinetoplast at a point a short distance from the posterior end. Undulating membranes are of moderate width and not greatly convoluted. Granules of volutin may or may not be present in the cytoplasm.

Trypanosomes in the cerebrospinal fluid (in the later stages of the disease) show marked want of uniformity in size and shape—involution forms of no special significance.—Wenyon.

Classification of Trypanosomes. *T. rhodesiense* and *T. brucei* are the same species, and *T. rhodesiense* is the name given to strains of *T. brucei* that can utilise man as a host, the majority of strains of *T. brucei* being incapable of so doing. The selection is exercised by the trypanosome rather than by the mammalian host.—H. L. Duke, "Final Rept. League of Nations Int. Com. on Human Trypanosomiasis," 1928.

As a means of differentiation, it is stated that *T. gambiense* is capable of affecting *G. palpalis* and only rarely *G. morsitans*, whereas the reverse is the case with *T. brucei* (*T. rhodesiense*), though in the blood of man the two trypanosomes resemble one another closely.—Wenyon.

Sir David Bruce classifies African trypanosomes pathogenic to man and animals on morphology, pathogenic action on animals, and mode of development in the insect host. With exception of *T. evansi* and *T. equiperdum*, all are carried from sick to healthy animals by **tsetse flies**. The first of the three groups into which they are divided includes *T. brucei*, *T. gambiense*, *T. evansi*, and *T. equiperdum*. The second comprises *T. pecorum* and *T. simiae*. The third embraces *T. vivax*, *T. capræ* and *T. uniforme*. (*T. vivax*, *T. capræ*, and *T. uniforme* resemble one another closely, differing only in their average dimensions. It is questionable whether they are distinct species or merely varieties of *T. vivax*).—Wenyon.

The development of the first group begins in the intestines of the fly and ends in its salivary glands. In the second it begins in the gut and ends in the proboscis. In the third the whole development is limited to the proboscis and does not occur at all in the intestines of the fly.—*Lancet*, ii/1914, 1373; *Pharm. J.*, i/1915, 33. See also *Lancet*, i/1915, 1323; ii/1915, 1; ii/1915, 55; ii/1915, 109. Trypanosomes, Some remarks on Classification, by H. M. Woodcock.—*Lancet*, i/1920, 462.

Animal Trypanosomes. *T. brucei* of Uganda is usually non-pathogenic to cattle of Uganda, and *T. vivax* usually has negligible pathogenicity, while *T. congolense* causes heavy mortality, but by passage mechanically from ox to ox it loses its virulence and becomes non-pathogenic. Transmission occurs readily in the absence of the tsetse fly. No satisfactory method of diagnosing chronic cases exists, yet it is believed that it is usually from the relapses of such animals that many outbreaks in Uganda arise. Tartar emetic satisfactory in *T. congolense* infection, but fails to cure in some cases and leaves "premunized" animals which may be the source of future outbreaks. No satisfactory treatment yet found for *T. vivax* infection.—U. F. Richardson (Uganda Vet. Service), *Trans. R. Soc. trop. Med. Hyg.*, Aug. 1928, 143.

T. evansi causes the disease "surra" in elephants, camels, horses, etc., in India and Africa. The carrier of surra has not yet been identified. There are no tsetse flies in India. Details of differences between *T. evansi* and *T. brucei* are given.—Sir D. Bruce, Roy. Soc., per *Nature*, Lond., 1911, 539.

T. grayi identified with the crocodile trypanosome, *T. kochi*, infection of the crocodile taking place through its mouth, the incubation period being 4 days. The correct name of the crocodile trypanosome is *T. grayi*. Monitors found not to harbour trypanosomes.—C. A. Hoare, *Trans. R. Soc. trop. Med. Hyg.*, 1929, 54.

Trypanosoma lewisi—the common rat trypanosome, is akin to the trypanosome of sleeping sickness.

Infection with this trypanosome is now known to take place by uninfected rats eating the dejecta of fleas, or the fleas themselves previously fed on infected rats. Yamasaki (1924) claims that the dog flea is able to infect by its bite by regurgitation from the stomach.—Wenyon.

Staining. Staining is best conducted with **Leishman's Stain**, *q.v.*; some beautiful specimens can be made with this by first pouring on to the film and allowing to stain half a minute, then adding twice the volume of distilled water and allowing to stain further half an hour. Wash in distilled water and dry in customary manner.

Other methods of staining are with thionin blue, methylene blue, Giemsa's stain and Borrel's blue, *q.v.*

Manson recommended the examination of the blood when the temperature is high; it is well to centrifuge as the trypanosomes accumulate in the leucocyte layer above the red corpuscles.

Laveran's Method of Staining Trypanosomes. Prepare thin blood films and fix in absolute alcohol 5 to 10 minutes. The following are required:—

- (1) *Solution*:—Methylene blue and silver oxide (Borrel's blue). Prepare "some" silver oxide freshly by means of silver nitrate and sodium hydroxide. Wash the precipitate with distilled water thoroughly, and add to it a saturated solution of medicinal methylene blue. Allow to remain for a fortnight, occasionally shaking.
- (2) Aqueous solution of eosin, 1 per 1000.
- (3) Solution of tannin 5%, or, better, a solution of "Tannin Orange."

Mix just before use: No. 1 solution 1 ml., No. 2 solution 4 ml., distilled water 6 ml.

Stain in a flat dish, film downwards, for 5 to 20 minutes—5 to 10 minutes is enough in most cases. Wash in water and treat with tannin for a few minutes. Wash in water and then in distilled water. If precipitate found on the preparation, wash in clove oil and brush off with xylol.

Cultivation. Cultures of *T. gambiense*, *T. rhodesiense* and *T. brucei* obtained with Ponselle's medium (*q.v.*), using the same sodium chloride concentration. Rabbit serum may be replaced by monkey serum for cultivation of pathogenic trypanosomes of African mammals. When inactivating the media for the cultivation of pathogenic trypanosomes in the higher mammals it is well to increase the temperature from 70° to 75°.

Trypanosomes cannot exist in a medium contaminated by bacteria. Efforts to obtain positive cultures from blood and cerebrospinal fluid of little value as a diagnostic method. The complement-fixation test should furnish more fruitful results than the precipitin test in identifying the blood found in the alimentary tract of glossinæ.—M. Maximo Prates, "Final Rept. League of Nations Int. Com. on Human Trypanosomiasis, 1928."

Transmission. In man it is transmitted from the sick to the healthy by a tsetse fly (usually *Glossina palpalis*). In the stomach of this fly the trypanosome multiplies by fission.

Human trypanosomiasis never spreads in the absence of Glossina and this is the only insect in which the trypanosomes are known to develop cyclically. The virulence of the strain appears to be entirely independent of its transmissibility. A consideration of the factors which may influence the transmissibility shows that of four possible explanations of inhibitory effect—the fly, the climate, the host, and the trypanosome itself—the transmissibility of a trypanosome by a glossina is a function inherent in the trypanosome itself. Different strains of *T. gambiense* show great differences in cyclical transmissibility by *G. palpalis*, and it is justifiable to infer that at any stage of infection of man by *T. gambiense* the transmissibility of the trypanosome by *G. palpalis* may be lost. Its transmissibility diminishes when the strain is introduced into a sheep or goat and after some months in these animals it loses its transmissibility altogether and it is improbable, therefore, that these animals play any important part as reservoirs of this trypanosome; calves also are a negligible factor. *T. gambiense* may lose its transmissibility quite suddenly on transfer from one host to another by cyclically infected *G. palpalis*.—H. L. Duke, "Final Rept. League of Nations Int. Com. on Human Trypanosomiasis," 1928.

There is little or no evidence to incriminate wild game as reservoirs of this trypanosome. Though it undoubtedly originated from a trypanosome of animals (probably *T. brucei*) it has now become adapted to man to such an extent that there is little tendency for it to infect game.—Wenyon.

Yorke, Adams and Murgatroyd have found that normal human serum or citrated plasma has pronounced trypanocidal action *in vitro* on *T. rhodesiense* and other species except *T. gambiense*, and they believe that man's immunity to the various animal species is due to this property. Lethal effect on *T. rhodesiense* is surprising. They believe *T. gambiense*, like *T. rhodesiense*, is identical with *T. brucei*, its differences being due to profound modification on numerous passages through man. The natural host is wild game and the game trypanosome is not pathogenic to man because of the protective action of his blood, but under certain conditions the trypanocidal substance is destroyed and he becomes susceptible. When *T. gambiense* is passed to game or domestic

animals it quickly loses its serum resistance and becomes capable of infecting normal man. If this hypothesis is confirmed it may have a great bearing on methods of eradication and control.—*Ann. trop. Med. Parasit.*, 1930, per *Brit. med. J.*, ii/1930, 1094.

Epidemiology in the *G. palpalis* and *T. gambiense* Areas. The endemic in the Semilki area is serious, the virus showing a tendency to spread, creating fresh foci in the *palpalis* distribution area. There is every likelihood that the endemic will spread beyond its present limits and that the virus may spread through neighbouring territories, the natives possessing no safeguards and being themselves the first to spread it owing to migratory habits and racial ties. The effects of the chemical prophylaxis are thus checked, and will be until the movements of persons and traffic are supervised.

In the Upper Uele district (Belgian Congo) the efforts of the Medical Service during the past 3 years have been crowned with success, and the disease is abating, the causes being complete census of the natives, chemical prophylaxis, creation of a road system, and the prohibition of certain areas. There is no likelihood of the disease spreading to any considerable extent in this area during the near future.

It seems that the "danger zones," the reservoirs of trypanosomes, are extremely small in area, and are easy to destroy. Endeavours should be made to discover these reservoirs.—L. Van Hoof and H. L. Duke, "Final Rep. League of Nations Int. Com. on Human Trypanosomiasis," 1928.

General Recommendations for the Control of Sleeping Sickness. The movement of natives should be controlled. This implies: a census; the use of an identity card and passport by each native; delimitation of areas, entry into and departure from which are contingent on possession by a native of a visa stating he is free from trypanosomiasis; legislation to give force to these regulations and the endowing of medical authorities with judiciary powers; an international agreement for the control of the disease on frontiers; the establishment of observation posts for examination and control of visas.

There should be compulsory treatment for infected natives. Heavily infected zones should be evacuated. Clearing measures are costly and of little permanent value; in *palpalis* regions they should be restricted to much-frequented places and must be thorough and well-maintained.—F. K. Kleine, L. Van Hoof, and H. L. Duke, *Trop. Dis. Bull.*, 1928, 759-781.

Treatment. With regard to therapeutics, **Tryparsamide is remarkably efficacious** and should be used systematically in all cases where possible; sulphoxyl-salvarsan and bismuth-tryparsamide of no practical value, and Bayer "205" should be reserved for arsenic-fast cases and, provisionally, as a preventive for natives exposed to infection.—L. Van Hoof and H. L. Duke, "Final Rept. League of Nations Int. Com. on Human Trypanosomiasis," 1928.

Germanin (Bayer "205"), if given in the early stage of infection by *T. gambiense* is curative, but in *T. rhodesiense* infection results are less certain. Tryparsamide is the drug of choice where the central nervous system is implicated. Present tendency in British territories in Africa is to give first Germanin and later Tryparsamide.—"Tsetse Fly Committee Rep." (1925-1931), *Brit. med. J.*, i/1933, 333.

Drug Resistance. *In vitro* experiments show that the organic pentavalent arsenical and antimonial compounds are but slightly trypanocidal, a solution of 1 in 1600 being required to destroy the parasites within 24 hours; the organic trivalent arsenical compounds are extraordinarily trypanocidal even when diluted several hundred million times, as are also the arsenobenzols; sodium arsenite and tartar emetic also display considerable activity. As the pentavalent compounds have little trypanocidal power they must be reduced in the body of the host to their trivalent forms. If a strain of trypanosomes becomes resistant to any of the aromatic compounds of arsenic or antimony it likewise becomes resistant to all the other commonly employed aromatic compounds, but not to the non-aromatic compounds of arsenic and antimony, and it is misleading to refer to "arsenic resistance" or "antimony resistance"; the resistance is to the various substituted phenyl radicals of the aromatic compounds. Drug resistance is a character inherent in the trypanosomes themselves. Whereas a normal strain of *T. rhodesiense* is killed by a solution of 1 in 100,000,000 of reduced tryparsamide in 24 hours at 37°, the resistant strain withstands a solution of 1 in 400,000—they owe their resistance to the fact that they do not absorb aromatic arsenicals. This drug resistance is fundamentally a process of mutation and is easier to produce

by the aromatic compounds, Atoxyl, Tryparsamide, Arsacetin and Stibenyl, than by Halarsol and neoarsphenamine, while its production by Bayer "205" is a tedious and lengthy matter, and it seems impossible to produce it at all with tartar emetic. The rapidity of production of drug resistance is dependent on the size and spacing of doses, the quickest and most certain method being to give daily such doses as just fail to clear the peripheral blood of parasites; it is highly probable that the reproduction of a resistant strain in man is of frequent occurrence. Resistance is slow at first but develops with great rapidity till a condition of complete resistance is reached, when further doses of the drug have not the slightest effect on the infection. It has been shown that cases which are not cured by the first course of Tryparsamide cannot be cured by further dosage with the drug.—Warrington Yorke, *Brit. med. J.*, ii/1932, 668.

Sudden or rapid death was frequently the termination of cases of sleeping sickness treated with full courses of Atoxyl.

J. O. Shircore suggests the possibility in *T. rhodesiense* infection of an uninfected cerebrospinal fluid becoming infected with trypanosomes from the blood carried by the needle in lumbar puncture, or by bleeding from the vessels of the spinal membranes damaged by passage of the needle, and further suggests that the blood should previously be cleared up by Bayer "205," Atoxyl, tartar emetic.—*Trans. R. Soc. trop. Med. Hyg.*, Feb. 1928.

Lumbar puncture may be dangerous, especially if repeated in patients with *T. rhodesiense* infection, not only from the likelihood that blood from vessels ruptured by the puncture may carry trypanosomes from the vessels into an uninfected cerebrospinal fluid, but principally because the blood which escapes into the cerebrospinal fluid may increase the albumin content of the latter sufficiently to allow of their surviving in it parasites which have reached it from the choroid plexus, which is actually the seat of the early invasion of trypanosomes. Further studies are necessary on the degree of persistence of albumin artificially introduced into the cerebrospinal fluid and its influence on invasion by the parasites.—M. Peruzzi, *Trans. R. Soc. trop. Med. Hyg.*, 1928, 95.

See also Organic Antimony and Arsenic Compounds (Vol. I) for recent treatment.

Prophylaxis. A consideration of the evidence now available suggests that a single dose of 1 g. of Bayer "205" intravenously will protect a man for at least 113 days from infection by tsetse carrying cyclically *T. rhodesiense*, the protective effect being enhanced by a second dose 2 or 3 weeks after the first. Also it seems probable that within certain, at present undefined, limits the protective effect may be directly proportional to the number of doses given and that the natural sensitiveness of the mammal to the trypanosome plays an important part in determining the duration of the protection conferred, the more susceptible monkey receiving less protection per dose per kilogramme body weight than the more resistant man. It is probable though not yet proved, that the protection conferred by Bayer "205" is greater against *T. rhodesiense* than against *T. gambiense*. At the present time, to be on the safe side, a prophylactic injection of 1 to 1.5 g. of Bayer "205," repeated every 3 months while exposure to infection lasts, is recommended.—H. L. Duke, *Lancet*, i/1934, 1336.

Tuberculosis. Recognition of *B. tuberculosis*. Delicate, straight, or more usually slightly curved rods. When stained usually beaded in appearance. The length of the organism commonly said to be about one-quarter to one-half the diameter of a red blood corpuscle, but it varies considerably. Involutive and branching forms occasionally met with. Gram-positive.

The tubercle bacillus is about 1 μ in length when grown in blood serum and from 1.25 to 6.5 μ in the tissues.

Present in large numbers when the process is acute, but relatively scanty or absent in chronic forms of tuberculosis, e.g., caseo-non-suppurating glands, lupus, etc.

Tubercle bacilli contained in sputum retain their vitality for considerable time even when the sputum dries up.

To obtain satisfactory specimens of sputum. Tubercle bacilli are often not found in sputum owing to bad specimens. An active cough reflex may be excited by sniffing vapour of essential oil of mustard from neck of bottle containing a small quantity. When this fails intralaryngeal injection by syringe of a few drops of a weak solution of sodium bicarbonate to which is added a little hydrogen peroxide; or alternatively transnasal instillation of a few drops of the solution. The administration for a few days of potassium iodide also facilitates expulsion of sputum.—Sir J. Dundas Grant, *Brit. med. J.*, i/1928, 628.

STAINING METHODS

Ziehl-Neelsen method: Sputum and sections.—1. Prepare film from sputum or a section ready for staining, and fix by usual methods. 2. Heat filtered carbol-fuchsin in a test-tube and cover specimens with it entirely; stain films 5 minutes, sections 10 minutes. (**Carbol-Fuchsin Solution**, Neelsen's solution, is prepared by mixing concentrated alcoholic fuchsin* solution 1 with 5% phenol solution 9, slightly warmed.) 3. Wash well in water. 4. Decolorise almost completely by immersing in 25% sulphuric acid. (If 3% hydrochloric acid in 95% alcohol be used instead, smegma and similar organisms are excluded). 5. Wash well in water. 6. Counterstain with alkaline methylene blue or carbolised methylene blue. 7. Wash, dry and mount in xylol balsam (sputum). 8. If section, dehydrate with alcohol, clarify with xylol and mount in xylol balsam. If dehydrated with aniline instead of alcohol a clearer preparation is produced.

Examine wherever possible the first sputum expectorated after the night's sleep.

Alkaline methylene blue is prepared by mixing saturated alcoholic methylene blue solution, 142 m., with 1 oz. of a 1 in 10,000 solution of caustic potash. (Note.—Medicinal methylene blue is far more soluble than ordinary and should be used.)

Carbolised methylene blue is prepared by dissolving methylene blue 1 as much as possible in alcohol 90% 7, adding phenol solution 5% 70, allowing to settle and decanting.

Acid-Fast Bacteria. In addition to *B. tuberculosis*, *B. lepræ* (q.v.) and the smegma bacillus which resist acid by the Ziehl-Neelsen method the following organisms give identically similar reaction.

1. *Timothy grass bacillus*, syn. Moeller's grass bacillus, producing lesions closely resembling tubercles. Another variety of this organism has been found in the dust of hay lofts, and a third variety is known as the "Mist bacillus" (dung bacillus).

2. *Petri-Rabinowitch butter bacillus* producing lesions closely allied to tuberculosis when injected into the peritoneal cavity of guinea-pigs.

Only in the case of material where outside contamination has been possible do these bacilli become an element for consideration—i.e., the customary method of examination is practically of unvarying value—Muir and Ritchie.

Acid-fast organisms (but not alcohol-fast) present in every case of true atrophic rhinitis (ozæna) but in no other disease of the nose. The Ziehl-Neelsen stain is only roughly diagnostic and not so precise as picro-fuchsin which emphatically excludes all bacilli which are only acid-fast.—W. Wyatt Wingrave.

To Exclude Acid-fast Bacilli and all other Bacteria except Tubercle and Leprosy

1. Wash film in alcohol after fixing by radiant heat.
2. Stain with hot carbol-fuchsin.
3. Differentiate in 25% sulphuric acid and wash freely in tap water and alcohol.
4. Counterstain in picric acid and alcoholic solution. Dry and examine by 1/12 inch immersion lens.—Wyatt Wingrave.

*Distinguish fuchsin from **acid fuchsin**, syn. **Fuchsin "S," acid magenta**, a mixture of the ammonium and sodium salts of trisulphonic acids of rosaniline and para-rosaniline.

Rapid Staining Method. Spread material on slide, apply Ziehl's carbol-fuchsin, heat slide till it steams, and wash in running water. Then place for 40 to 50 seconds in a solution of: brilliant yellow 0.15 g., concentrated sulphuric acid 10 ml., alcohol 20 ml., and distilled water 85 ml. Again wash and dry with blotting paper. The bacilli are coloured red on a lemon-yellow background. Only takes half the time of Ziehl's method, the bacilli are clearer and more numerous, and it is just as reliable as the Ziehl-Neelsen test.—*P. Doglio, per J. Amer. med. Ass., ii/1932, 514.*

Spengler's Method. (1) Stain with carbol-fuchsin, steaming for 3 to 5 minutes, (2) pour off carbol-fuchsin and apply picric acid alcohol (2 g. picric acid in 40 ml. distilled water; stand for 24 hours, filter and add equal vol. 96% alcohol) for 2 to 3 seconds, (3) apply 3 to 4 drops of 15% nitric acid for 5 seconds (4) pour off and apply picric acid alcohol till sputum looks yellow, (5) wash, dry and mount. Considered by many superior to all other methods.—*Stitt.*

Rosolic Acid Method. Specially for *B. tuberculosis* in tissues. Stain in hot carbol-fuchsin for 5 minutes. Wash quickly in tap water. Dip five or six times in saturated alcoholic solution of rosolic acid (corallin) till fuchsin is removed. Wash in water and counterstain in saturated alcoholic solution of methylene blue.

Konrich's Method. Stain with hot carbol-fuchsin for $\frac{1}{2}$ to 2 minutes, rinse with water, decolorise with 10% sodium sulphite solution for $\frac{1}{2}$ to 1 minute, rinse with water, then counterstain with malachite green (50 ml. of saturated aqueous solution of malachite green in 100 ml. distilled water) for $\frac{1}{4}$ to 1 minute.—*Yearb. Pharm., 1922, 39, 40.*

Harrison's (L.E.) Stain consists of 1 g. of basic fuchsin added to 100 ml. of distilled water. To 75 ml. of the filtrate is added 10 ml. of 37% Liquor Formaldehydi, 10 ml. saturated aqueous solution of phenol, and 5 ml. of glycerol. Stains tubercle bacilli and Vincent's organisms a brownish-black against light yellow-brownish background.—*J. Lab. clin. Med., per J. Amer. med. Ass. ii/1925, 636.*

Fuchsin-Aniline Green Method.

Solution A. Fuchsin 10, absolute alcohol 100.

„ B. Strong ammonia solution 3, water 100.

„ C. Water 80, nitric acid 20, malachite or iodine or acid green 10 g.s. to saturate. Methyl green does not give satisfactory results.

Add one part of A to 10 of B. Warm until vapour arises, immerse 1 minute, wash with water, then immerse in C 40 seconds. Wash off thoroughly. Bacilli red on pale green ground.

Safranin Method. A solution consisting of 100 ml. of distilled water, 10 ml. of N/10 sodium hydroxide and 4 g. of safranin is better than carbol-fuchsin for liquid sputum. Bacilli stained a brilliant red over a dull deep red.—*Ransom J. Amer. med. Ass., i/1929, 1306.*

Ligroin Method of Detection. To 5 ml. of sputum in a flask add 50 ml. of caustic potash solution 5%. Shake and leave at room temperature until the sputum is homogenised. Dilute with 50 ml. of tap water and shake again. Add 2 ml. of ligroin and shake until emulsion is formed. Warm to 60° until evidence of layer of smaller bubbles on the surface. A number of drops are then taken from immediately below this superficial layer and placed on a warm slide. The dry film is then fixed with saturated sublimate solution and stained by Ziehl-Neelsen method.—*Lancet, ii/1910, 1747.* The ligroin causes the tubercle bacilli to rise to the surface of the meeting of the two liquids.

Loeffler's Modified Antiformin Method. (Antiformin, a hypochlorite disinfectant, can be used to isolate the bacillus from the sputum). To 5 to 20 ml. of sputum add equal volume of Antiformin 50% diluted with water. Heat until clear liquid results. To 10 ml. of the mixture add 10% solution of chloroform in alcohol (5 ml. generally suffices). After shaking, centrifuge 15 minutes. An opaque layer is then formed between the chloroform which occupies the bottom of the centrifuge and the supernatant fluid. Pipette off the latter and remove the opaque layer wholly on to a slide. Make films, fix and stain. The method is said to be rapid and simple and to give good results.—*Lancet, ii/1911, 1747.*

Alternatively, the sputum is mixed with an equal quantity of a 30% dilution of Antiformin, and the mixture incubated overnight at 37°. After centrifuging the fluid is poured off and replaced by an equal bulk of normal saline. After

shaking up, again centrifuge. Films from the deposit thus washed adhere better to the slide. Its use is justified by small percentage of "corrections."—*Brit. med. J.*, ii/1912, 411.

Antiformin digestion of sputum, followed by centrifuging and examining the sediment, revealed tubercle bacilli, which could not be seen in the simple smear in 22 cases. Antiformin method more efficient by 9%.—*Per J. Amer. med. Ass.*, ii/1925, 226.

Glycerin most useful for isolating acid-fast bacilli from contaminated material, e.g., tubercle bacilli in tissues (also in sputum) preserved in glycerin remain alive for months, possibly years, in cold storage.—C. C. Twort, *Lancet*, i/1922, 1221.

B. tuberculosis in Fæces. Formerly it was thought that the discovery of *B. tuberculosis* in fæces was diagnostic of tuberculosis enteritis—the bacillus, however, frequently occurs in fæces of patients suffering from pulmonary tuberculosis.

Acid-fast bacteria resist Antiformin when diluted to 20% for 2 to 5 hours—other bacteria and organic matter generally are speedily dissolved. A small piece of fæces (about a cubic $\frac{1}{2}$ inch in size) is placed in a conical glass and to this some 20 ml. of Antiformin diluted with water to 15% is added and the whole well mixed. More of the diluted Antiformin is added and the mixture allowed to stand for about an hour. A white curdy precipitate appears on mixing and settles. Beneath this white layer some unchanged fæcal matter remains and above the white layer the fluid is of a clear yellow or brownish colour. A drop or two from the white curdy layer is mixed with a drop of albumin water and stained by the Ziehl-Neelsen method. Much searching may be necessary. For certainty, alcohol may be used in addition to acid for decolorising.—*Brit. med. J.*, ii/1910, 84; *Lancet*, ii/1910, 1747. See also *Brit. med. J. Epit.*, i/1910, 36.

B. tuberculosis in Urine. At least six films should be prepared. The specimen is centrifuged, the supernatant liquor is poured off, and the sediment is washed two or three times by shaking up with sterile water, centrifuging on each occasion. Fix film with alcohol. Stain as for sputum, by picric acid method. Always wash film with albumin water before staining.

B. tuberculosis in Pus. Tubercle bacilli can be found microscopically in well over 90% of specimens of tuberculous pus from lesions of bones and joints. Half-saturated watery picric acid the best counterstain—restores red colour to feebly acid-fast bacilli otherwise invisible or unrecognisable.—A. D. Gardner, *Lancet*, i/1926, 1090.

B. tuberculosis in Blood. Tubercle bacilli according to Leibermeister can be demonstrated in the blood in every case of open pulmonary tuberculosis, and in many cases of early disease.—*Brit. med. J.*, i/1923, 1055.

B. tuberculosis in Milk. In spite of supervision it is no doubt true that a very large proportion of samples of milk supplied currently for human consumption are tuberculous. The staining is similar to that used for urine. Both the cream and the sediment must be carefully searched on centrifuging. It is well to soak the slides at the outset, after drying and fixing, in ether for a minute or two to remove the fat. Stain by picric acid method to exclude butter bacilli. *Negative results in all instances are not necessarily conclusive of absence of infection.* Injection of susceptible animals is then necessary for confirmation. See also *Milk Analysis* this volume.

CULTIVATION

B. tuberculosis was first grown on blood serum by Koch, but will not grow without addition of glycerin to the ordinary media. Requires temperature of 37°. Dry wrinkled growth, somewhat like a lichen, on glycerin agar in 3 weeks. Cultures, especially in glycerinated broth, have fruity odour.

To obtain a pure culture of the organism from tubercular material it is necessary to inoculate guinea-pigs with same, and after a lapse of 4 to 6 weeks cultures are made from enlarged glands direct on to blood serum or glycerin potato. Glycerin agar is not recommended for use direct *post mortem*, but the organism flourishes on this on sub-culture.

A diagnosis of pulmonary tuberculosis based on a single positive direct sputum examination is not justified. Even when the clinical picture is convincing the finding of acid-fast bacilli in the sputum is not necessarily proof-positive of tuberculosis. The importance of cultural verification in all doubtful

cases cannot be too strongly stressed. The practice should be adopted of indicating in every sputum report an approximate number of the tubercle bacilli present.—G. G. Kayne, *Brit. med. J.*, i/1934, 755.

An acid medium apparently favours the growth of the tubercle bacillus while an alkaline medium appears to be unfavourable. Steapsin or lipase made alkaline and mixed with a strong cohydrolizer of wax, decorticates the tubercle bacillus, as does also a similar insulin mixture. Further experiments in progress using ozone and activated oxygen as adjuncts. Also experiments in which tubercle bacilli, subjected to the decorticating action of steapsin and insulin with chloroform as cohydrolizer, are being used as a bacterin.—*J. trop. Med. (Hyg.)*, Dec. 15, 1924, 348.

Sulphuric Acid-Crystal Violet-Potato Cultivation Method. Take 1 ml. of the specimen, whether sputum, urine, or tissue, beat to a homogeneous pulp and place in a 15 ml. sterile centrifuge tube with 1 ml. 6% sulphuric acid. Stopper with sterile cork and incubate at 37° for 30 minutes, shaking occasionally. Dilute contents with 10 ml. sterile 0.9% sodium chloride solution, well mix and centrifuge. Decant supernatant fluid and seed the residue on to the surface of the crystal violet-potato medium. Cap culture tube with tin-foil after cotton plug has been impregnated with hot paraffin. Prepare medium by cutting large clean peeled potatoes into cylinders 3 inches long and 5/8 inch diameter. Halve cylinders longitudinally and soak immediately for 1 to 2 hours in 1% sodium carbonate solution containing 1 in 75,000 (0.0015%) crystal violet (mix just prior to use). Then gently wipe cylinders and place in sterile culture tube containing 1.5 ml. 5% glycerol broth cotton plugged, and sterilise in autoclave for 30 minutes. After incubation on this medium for 2 to 6 weeks a luxuriant elevated growth of tubercle bacilli becomes visible when positive. Equal in efficiency to the guinea-pig inoculation method and is recommended as a substitute for diagnostic purposes as it has many practical advantages. The medium found better than Dorset's egg medium and others, for favouring growth of tubercle bacilli when present in small numbers.—H. J. Corper, *J. Amer. med. Ass.*, ii/1928, 375; *ibid.*, i/1929, 1353, 1886.

Peptone Culture Medium. The use of a medium consisting of the products of pancreatic digestion of beef, glycerol, dextrose and salts, is advocated. *Ann. Inst. Pasteur*, 1926, 746; *Brit. chem. Abstr.*, 1926, A1062.

A blood culture method for *B. tuberculosis*.—E. Lowenstein, *Ann. Inst. Pasteur*, 1933, 161, per *Brit. med. J. Epit.*, ii/1933, 18.

Cruickshank employs Antiformin for isolation of the bacillus, then inoculation of glycerinated egg medium with centrifuged sediment. The bovine bacillus grows best *without* glycerin.—*Brit. med. J.*, ii/1912, 1298.

DIAGNOSIS

Old Tuberculin. Standard. There is an International Standard for old tuberculin kept in the Serum Institute in Copenhagen. The British standard which has the same activity, is kept in the National Institute for Medical Research, Hampstead. There is no unit of activity for old tuberculin.

Method of Comparison. To compare unknown samples with the standard guinea-pigs are sensitised by injecting them intramuscularly with 0.25 mg. or 0.5 mg. of living bacilli from a 3 weeks' growth of *B. tuberculosis*. Sensitisation follows in 3 weeks. Injections are then made into the shaven skin of the flank of the guinea-pig. On one side dilutions of the standard are injected, the dilutions being 1 in 1000, 1 in 2000, 1 in 4000. On the other side similar dilutions of the unknown are injected. Twenty-four hours later the sites of injection are examined to compare the inflammatory reactions. Those produced by the unknown samples should be indistinguishable from those produced by the standard.

For details of diagnostic procedure and treatment see Vol. I.

Complement-fixation Test. Preparation of the Antigen. Use a young, rapidly-growing culture on a good medium (e.g., Dorset's egg). Inoculate 6 tubes and allow to grow for 10 to 14 days, scrape off growth, and prepare emulsion in a proportion of 1 g. of the bacilli to 50 ml. carbol-saline (0.25%); store the antigen in a refrigerator. As a rule 0.05 ml. to 0.1 ml. is required in the test.

The Test. (1) Estimation of the minimal hæmolytic dose (M.H.D.) of the complement. Place falling doses—from 0.35 ml. to 0.05 ml.—of the complement, diluted 1 in 24 with saline, in a series of test tubes: make the total volume up to 1 ml. with normal saline, and add 0.5 ml. of a 5% suspension of sensitised sheep's corpuscles (6 units of amboceptor) incubate tubes in water-bath

for 10 to 20 minutes and note the tube with the least amount of complement showing hæmolysis; two and a half times this amount is the complement required in the standardisation of the complement and in the actual test. (2) **Standardisation of the antigen.** Place falling doses of antigen—0.2 ml. to 0.025 ml., in a series of 6 tubes, adding $2\frac{1}{2}$ units (M.H.D.) of complement diluted to give a volume of 0.5 ml. to each, and add saline up to 1 ml.; shake tubes and incubate at 37° for one hour; add 0.5 ml. of 5% suspension of sensitised sheeps' corpuscles; shake tubes and place in water-bath for 10 to 20 minutes. The tube containing the largest quantity of antigen (usually 0.1 ml.) showing complete or nearly complete hæmolysis is the amount of antigen to be used in the test. (3) In the test, 0.1 ml. of patient's serum and of a control normal serum is used and five test-tubes filled as follows:—

Tube	Patient's Serum		Control Serum		Antigen Control V
	I	II	III	IV	
Antigen ...	0.1 ml.	—	0.1 ml.	—	0.1 ml..
Serum ...	0.1 „	0.1 ml.	0.1 „	0.1 ml.	—
Complement	0.25 „	0.25 „	0.25 „	0.25 „	0.25 „
Saline ...	0.55 „	0.65 „	0.55 „	0.65 „	0.65 „

After mixing, incubate tubes for one hour, then add 0.5 ml. of the sensitised red cells to each, shake, place in water-bath for 10 minutes and note occurrence of hæmolysis. Tubes II, III, IV and V should show complete hæmolysis and also tube I if the patient's serum is negative, but if positive there will be little or no hæmolysis in I. An examination of the literature shows that this test is highly specific.—Hewlett and McIntosh.

Complement-fixation reliable in diagnosis of an active or recently active tuberculous lesion. Negative result also reliable.—A. Lisle Punch and A. Fleming, *Lancet*, ii/1920, 647; ii/1924, 497. See also A. Sellers and E. N. Ramsbottom, *Brit. med. J.*, i/1921, 47.

In a communication to the Medico-Chirurgical Society of Edinburgh, A. N. Smith and F. Hewat stated the test might be of value in differentiating between an active and an inactive lesion. Sir Robert Philip considered the test of no essential value so far as initial diagnosis was concerned, but thought it might be in assessing the patient's condition from time to time. A. Rutherford, who had carried out 600 tests, considered the test of undoubted value in certain groups of cases, yielding a positive result when the clinical findings pointed otherwise, yet on later investigation correctness of the serum result was demonstrated.—*Brit. med. J.*, i/1924, 15.

Results of the test should carry some weight with the clinical observer and with a positive finding a very full investigation should be made before ruling out tuberculosis.—W. Broughton-Alcock and others, *Lancet*, i/1925, 1331.

Stomach Lavage Diagnosis in Children. Give 2 grains of potassium iodide three times daily for 2 days before the lavage. Encourage child to cough first thing in the morning for 20 minutes. Then give 100 ml. boiled water to drink. Fifteen minutes later pass stomach tube and withdraw as much fluid as possible. Centrifuge and treat the deposit with 1:10 Antiformin (4 ml. diluted Antiformin being added to 100 ml. lavage). Inject under the skin in the abdominal region of the guinea-pig. The guinea-pig is watched for 6 weeks and then killed and examined for tuberculosis both by direct smear of the diseased glands and by culture.

The value of the test is very largely in its definiteness; a positive result means definite tuberculosis.—W. R. F. Collis and C. F. Brockington, *Lancet*, ii/1933, 127.

Cases of destructive pulmonary tuberculosis showed 75% positive results as against 28% amongst clinically non-destructive lesions. Other forms of tuberculosis showed no positive results. It is concluded that a positive stomach lavage augurs a grave prognosis.—C. Kereszturi and co-workers, *J. Amer. med. Ass.*, i/1933, 1481.

Albumen in Sputum. To 10 ml. of fresh sputum add 30 ml. of 1% acetic acid and mix. Filter and test filtrate by Esbach's albuminometer.

The presence of albumen in the sputum, in the absence of pneumonia or pulmonary œdema, is very strong evidence of pulmonary tuberculosis. The quantity of albumen is proportional to the number of bacilli present—when there are 5 or fewer bacilli in 10 fields albumen is usually 0·06%, with 20 present it increases to 0·09%, with 50 to 0·1%, with 100 to 0·11%, and with 500 to 0·13% or more.—P. Moxey, *Practitioner*, ii/1929, 142.

Relationship Between Human and Other Forms of Tuberculosis

The Royal Commission on Human and Bovine Tuberculosis in its Report (1907-1911) found that the human and bovine types are *morphologically indistinguishable*, but cultural characters of the organisms differ, also the pathogenic effects on different animals.

Human bacilli produce: Pulmonary tuberculosis, tuberculous laryngitis, secondary intestinal ulceration, fistula in ano.

Bovine bacilli produce: Enlarged lymph glands, abdominal tuberculosis, lesions of bones and joints, meningitis, acute miliary tuberculosis, lupus, and rarely secondary extension to lungs.

The infections are antagonistic to each other and human and bovine bacilli are rarely found in the body at the same time.—N. Raw, *Brit. med. J.*, i/1927, 373.

The bovine tubercle bacillus can produce all the different forms of clinical tuberculosis and can set up tuberculous lesions in every organ and gland indistinguishable from those caused by the common human tubercle bacillus. It is certain that at the present time children are being infected with bovine bacilli which will later produce in some of those who escape early acute fatal disease the most serious of all forms of human tuberculosis, namely, phthisis pulmonalis.—A. S. Griffith, *Brit. med. J.*, ii/1932, 502.

The bovine bacillus could produce exactly the same kind of lesions as the human—dangerous to consider it less virulent. Koch was mistaken in thinking the bovine tubercle bacillus was not dangerous to man.—W. T. Munro, Discussion by Section of Tuberculosis, B.M.A. Cent. Meeting, 1932, *Brit. med. J.* ii/1932, 316.

HUMAN, BOVINE AND AVIAN TUBERCULOSIS DIFFERENTIATED. The human type is not confined to man or even to mammals, nor the avian type to birds while the bovine occurs in a large variety of animals, not excepting man himself. The test for specific virulence is usually limited to inoculation of the rabbit. Occasional failure in the resisting power of these animals to human tubercle bacillus. Useful tables are provided showing *inter alia* susceptibility of various animals to infection with the three types. The fowl and other domestic birds are insusceptible to human and bovine bacilli. Spontaneous tuberculosis in the dog is relatively uncommon. This animal is difficult to infect artificially. Both mammalian types are capable of infecting dogs, but the avian type never. Of the deaths attributed to tuberculosis of all kinds about 6·5% are attributable to bovine bacilli and therefore to infection coming from the cow, probably in the immense majority of cases through milk.—L. Cobbett, *Lancet*, i/1922, 979.

The figure for bovine infection in Manchester is 50%, the route of infection being as a rule via the digestive tract.—*Lancet*, ii/1921, 1277.

Bone tuberculosis in children. Out of 150 cases 27% bovine type.—Sir H. Gauvain, *Brit. med. J.*, i/1921, 201.

Tubercle bacilli derived from sputum by cultivation. Of 212 cases of phthisis pulmonalis in England and Scotland, 205 were the standard human type, 4 were atypical human, and 3 standard bovine. Antiformin method used for obtaining cultures. No other investigator in this country has cultivated from tuberculous sputum any but tubercle bacilli of human type.—A. S. Griffith, *Lancet*, i/1914, 721.

For further details re bovine tuberculosis and milk infection see *Milk Analysis* in this volume.

Tuberculosis in dogs is comparatively rare—it is almost invariably due to infection from a human source. The symptoms—emaciation, loss of strength etc., are easily recognised.—*Brit. med. J.*, ii/1913, 827. On the other hand the prevalent opinion that dogs are practically immune to tuberculosis is erroneous. In 3 years 165 cases were recorded, all being verified anatomically.

and bacteriologically. The disease is more prevalent among dogs in town than in country districts. Cats also are capable of infection, but are less frequently affected than dogs. Horses seem to be very rarely affected, scarcely one, in 15,000 cases examined, has been recorded.—Cadiot, *Pharm. J.*, i/1914, 287.

Saliva of little importance in the spread of tuberculosis, tubercle bacilli being found in only 1·5% of fairly strong patients. Cough spray the most dangerous channel of infection, the bacilli being found in 50% of cases.—*Brit. med. J. Epit.*, i/1925, 5.

Typhoid

Characters of *B. typhosus*. *B. typhosus* is a motile rod 4μ long, but length varies on cultivation; motility due to flagella, 12 to 16 in number. Gram-negative. Grows easily in ordinary media. Produces acid in glucose and mannite, sorbite in milk. No indole in peptone water.

B. typhosus is very susceptible to acidity. In wine it rapidly disappears, while wine added to water will reduce number if present. 20 ml. of vinegar per litre kills *B. typhosus* in one hour.

FLAGELLA STAINS

McCrorie's Stains. Solution A. Night blue 1 in dehydrated alcohol 20, alum 1 in water 20, tannic acid 1 in water 20. Mix and filter at once. Solution B. aniline fuchsine. To 100 ml. of saturated aniline water, add 10 ml. of dehydrated alcohol and 1 g. of fuchsine, or carbol-fuchsine diluted may be employed.

Van Ermengem's Stains. A. 1% osmic acid solution 100, tannin 18, water 45; B. silver nitrate solution 0·25% to 0·5%. C. gallic acid 1, tannin 0·6, potassium acetate fused 2, water 70.

Pitfield's Method. Solution A. Tannin 1 g., water 10 ml. Do not filter. Solution B. Saturated aqueous solution of alum 10 ml., saturated alcoholic gentian violet solution 1 ml. Filter and keep in a stoppered bottle. Fuchsine will answer the same purpose as gentian violet. Equal parts A and B mixed, heated to nearly boiling and employed to stain 1 to 3 minutes, wash in water, dry and mount.

Plimmer and Paine's Method (for flagella). Rub down tannin 10, aluminium chloride (cryst.) 18, zinc chloride 10 and rosaniline HCl 1·5 with alcohol 60% 10, then employ a further 30 of the alcohol. In use, the clean slide is baked and allowed to cool to blood heat and a drop of 18 hours' culture placed at one end and allowed to run down by tilting. The film must dry quickly. One part of the stain is mixed with 4 parts of water and after standing 60 seconds it is filtered on to the film and left on for a further 60 seconds, then washed rapidly. Finally stain with carbol-fuchsine 5 minutes, wash and dry.

CULTIVATION

Conradi evolved a method of early diagnosis of typhoid fever. Researches demonstrated necessity of keeping the blood in a fluid condition, so as to avoid the disinfectant action of those substances which become active on coagulation. Bile is employed for this purpose; in addition, the medium contains 10% of peptone and 10% of glycerin. The blood from lobe of the ear is drawn into a pipette containing a little bile and mixed with 2 ml. or 3 ml. of the peptone-glycerin-bile medium in the proportion: blood 1, medium 3. Incubate at 37° for 10 to 16 hours and make cultures on agar plates according to the Drigalski-Conradi formula. Diagnosis can be effected by this method in 26 to 32 hours and it is applicable as soon as the patient exhibits a febrile temperature.

Drigalski-Conradi medium consists of a nutrose-lactose-litmus agar containing 1% **nutrose** (a sodium caseinate compound), 1% peptone, 0·5% salt, 3% agar, 1·5% lactose, in a nutrient both made with 750 g. horse flesh to the litre, also 13% of Kubel and Tiemann's litmus solution and a trace (0·001%) of crystal violet. After incubation typhoid colonies are blue, glassy like dew drops, paratyphoid are similar, and *B. coli* are bright red and opaque.

"**Crystal Violet**," and neutral red, advocated for distinguishing colonies of *B. coli* (coloured red) from those of *B. typhosus* (also *B. enteritidis* Gaertner and others), coloured blue to purple. Medium contains sodium taurocholate to

inhibit growth of nearly all but intestinal bacteria. Lactose is another essential component of the medium since *B. coli* and congeners decompose it with gas formation.

B. typhosus is said not to grow in a medium containing 0.01% arsenious acid whereas *B. coli* will grow in a medium containing 1.5%.

Brilliant Green and Telluric Isolation Method for typhoid and paratyphoid bacilli. Make the usual smear cultures on plates of Endo's or MacConkey's medium. Simultaneously inoculate peptone water containing brilliant green. Employ in preference a series of tubes for each specimen, but when time prevents this, use a concentration of 0.5 ml. of 1 in 10,000 brilliant green in 10 ml. of medium. Incubate both and if typical colonies are not present or are scanty in the solid medium make sub-cultures from the green tubes into the above-mentioned solid media. Incubate.

Telluric acid is also advised, 0.4 ml. of 1 in 1000 solution, with varying amounts of brilliant green per 10 ml. of medium. *B. typhosus* can sometimes be recovered from fæces by this combination better than by brilliant green alone.—C. H. Browning and L. H. D. Thornton, *Brit. med. J.*, ii/1915, 248. See also *J. Path. Bact.*, 1914, 127, in which potassium tellurate is similarly advised.

The method is useful for detecting a number of carriers. **Brilliant green has a special inhibitory effect** on the colon bacillus as contrasted with typhoid and paratyphoid bacilli, whilst it has a powerfully bactericidal action on practically all other organisms. Telluric acid is included in the medium because it was found that certain organisms giving the ordinary reactions of the enteric group but differing from them in fermenting inositol, escaped the action of the brilliant green alone but were killed off by the addition of telluric acid. Browning's work supported.—A. Leitch, *Brit. med. J.*, ii/1916, 317.

Phenol and Bromocresol Purple as indicators in the bacteriological examination of stools. May be used in the preparation of lactose-agar plates for the isolation of members of the typhoid-dysentery group. Employed successfully with brilliant green in isolation of typhoid-paratyphoid group.—A. M. Chesney, per *J. trop. Med. (Hyg.)*, 1922, 105.

Endo's Medium. Beef extract 5 g., peptone 10 g., agar 30 g., distilled water to 1000. Dissolve on water-bath, adjust to neutral reaction to phenolphthalein, filter and sterilise. To make plates, prepare 10% anhydrous sodium sulphite solution and to 10 ml. of this add 2 ml. of fuchsine solution (basic fuchsine 10 g. alcohol 100 ml.) and steam 5 minutes in water-bath. To each 100 ml. of the agar mixture add 1 g. of lactose, dissolve on water-bath and add 0.5 ml. fuchsine-sulphite solution.

By placing a circle of blotting paper in the lids of the petri dishes before sterilising them, all the water of condensation is absorbed; this aids greatly in making successful cultures.

The use of the medium with agglutination test is expeditious in isolating *B. coli* and the paratyphoid organisms. *B. coli* (being acid-forming) are golden-metallic looking. *Streptococci* form crimson dots. Suspicious colonies (grey-coloured) are plated on to Hiss Medium.

Hiss Medium. Dissolve Lemco 5, sodium chloride 5, in distilled water 1000, autoclave at 120° for 5 minutes. Add washed agar 8, and melt in autoclave at 130° for 5 minutes. Add washed gelatin 80. Dissolve and cool to 45°. Clear with white of one egg at 120° for 5 minutes, filter and add 1% dextrose and sterilise in steamer 1 hour. Fill 5 ml. tubes and sterilise in steamer again. This medium remains solid at 37°.—F. B. Bowman, *Brit. med. J.*, ii/1917, 250.

Fermentation Reactions of *B. Typhosus*. W. J. Penfold, dealing with fermentation of lactose, peptone water and of **dulcite*** water by *B. typhosus* states it does not ferment arabinose. Fermentation of glycerin and papillæ formation on isodulcite.—*Brit. med. J.*, ii/1910, 1672. Raffinose, erythritol and adonite are not fermented.

The fermentation of lactose—or non-fermentation—provides important information as to the coli-typhoid organisms.

The non-lactose fermenters include the organisms of typhoid and paratyphoid, bacillary dysentery and acute bacillary enteritis, whilst fermenters

***Dulcitol** is synonymous with dulcite and **melampyrite**, $C_6H_8(OH)_6$, a sugar from *Melampyrum nemorosum* and other *M.* and *Euonymus* species. It occurs in white crystals soluble in water, slightly in alcohol.

include *B. coli* and its numerous subtypes, all of which are of minor importance by comparison with the highly pathogenic species met with among the non-lactose fermenters. There are, however, non-lactose fermenters—saprophytes—of no greater importance than *B. coli*.—H. H. Duke, *Lancet*, ii/1921, 1212, 1288.

The sodium salts of *d*-tartaric, *l*-tartaric, *meso*-tartaric, citric, fumaric, and mucic acids for differentiating bacteria where sugar reactions fail.—*Brit. med. J.*, ii/1926, 565.

Biochemical characters of certain bacteria when living in association or artificially mixed, e.g., the mixture of two species *B. typhosus* and *B. morgani* may produce gas in some instances, though one species produces only simple acidity, never gas, and the other neither acidity nor gas.—A. Castellani, *Brit. med. J.*, ii/1925, 735.

DIAGNOSIS

Widal's Reaction (Serum Diagnosis). Collect sample of blood in a small capillary pipette, and seal the ends, that nearest the blood being closed first. By pricking the lobe of the ear or the finger the blood will run into the tube by capillarity. The serum is allowed to separate, or the tube is centrifuged to cause as complete a separation as possible of corpuscles which may mask a reaction. The serum is blown out on to the corner of a slide and a platinum loopful is mixed with 9 loopfuls of normal saline solution, and one loopful of this 1 in 10 dilution is mixed with two loopfuls of typhoid broth, not more than 24 hours old, preferably filtered through ordinary filter paper. This 1 in 30 dilution is now examined as a hanging drop. Dilution of 1 in 50 and 1 in 100 should also be made. A control experiment must be conducted in addition.

Positive Reaction. Complete: Clumping of organisms and cessation of movement occurs as a rule in under 30 minutes, or may be instantaneous. **Partial reaction:** Sluggish movement providing the control is actively motile. **Negative reaction:** No alteration in one hour. Dilutions 1 in 100 should give same results in 50 minutes; if the time exceeds this the diagnosis is doubtful.

The reaction may also be performed in similar dilutions in sealed capillary pipettes (Wright). This constitutes the macroscopic method of applying Widal's Reaction.

Notes of Caution in Applying. The broth itself, or a control with normal serum, should first be examined to see that the organisms are freely motile and show no pseudo clumps, as clumps are sometimes present in the broth before the addition of the blood. The serum of persons having previously had typhoid may react even years after. This may cause confusion where a typhoid diagnosis had not been given. Again, if only slightly diluted, e.g., 1 in 10, normal serum frequently "clumps," which is not the case on further dilution—1 in 30 or 50 is safest. Some workers require a result with a 1 in 200 dilution within half an hour to be positive. Too great a dilution may obscure. The blood of *all* cases does not react, case may be too early (generally obtained about end of first week). Cases are recorded where reaction intermits, absent one day, present next, and again recurs, and also a few described where there was no reaction throughout the disease, but these are fortunately very rare.

A special culture should always be at hand—one known to react, since occasionally laboratory cultures do not respond.

Anomaly in the Reaction. In examining blood of patients suspected of enteric group infections using Dreyer's Standard Method, "Zone phenomena" were frequently seen, i.e., the occurrence of agglutination in higher dilutions of a serum while lower ranges failed to agglutinate. It is more striking by the macroscopic (Dreyer) method than by the microscopic. It was found that the addition of another serum, non-agglutinating, to the bacillus under test increases the zone of inhibition. The presence of salt in the test augments but does not cause the negative zone.—A. F. S. Sladden, *Lancet*, ii/1916, 272.

Macroscopic Agglutination. The following is a convenient method: make dilutions of serum in ordinary test tubes, take a loopful of growth from an 18 to 24 hour old agar culture and emulsify in the dilution in the first tube, repeat in the second tube and so on. Make a control in normal salt solutions. Incubate and look for precipitates. A fine curdy flocculent precipitate indicates agglutination and a uniformly turbid emulsion a negative reaction.—Stitt.

The value and limitations of the agglutination tests in the diagnosis of the enteric group of organisms.—A. B. Rosher, *Lancet*, ii/1928, 461.

Colloidal Silica. Has power to inhibit action of complement, and thus prevent lysis and destruction by bacteria of blood fluids. Experiments with fresh blood on typhoid bacillus.—W. H. Tytler, *Brit. med. J.*, ii/1922, 980.

Atropine Injection as a Means of Diagnosis of the typhoid group in affections. Atropine 1/33 grain hypodermically barely increases the pulse rate in typhoid and paratyphoid "A" and "B" infections, whilst in normal people and those suffering from other diseases it accelerated it. At least one hour should elapse after a meal. Give the injection and allow 25 minutes to elapse—patient remaining absolutely quiet before making second observation. As an arbitrary rule an increase of pulse rate by about 20 or more beats a minute after the injection may be accepted as an indication that patient is probably not suffering from typhoid or one of the paratyphoid series. If the increase is only 10 beats or less the reaction is suggestive of infection.—H. Fairley Marris *Brit. med. J.*, ii/1916, 717; ii/1917, 492. For the details of the method, see *Spec. Rep. Ser. med. Res. Comm.*, No. 9, 1917, *Lancet*, ii/1917, 503.

Marris's Atropine Test of distinct and definite value in diagnosis of typhoid but of little value in paratyphoid group of fevers.—M. L. Treston, *Indian med. Gaz.*, 1926, 479 and 588.

Petzetakis's Iodine Reaction, a modification of, for diagnosis of typhoid fever. 25 ml. of urine are saturated with 20 g. of crystallised ammonium sulphate. After 15 minutes, filter urine and dilute to one-third if too thick. To 10 ml. of filtrate add one-fifth its volume of a 10% solution of sodium hydroxide and then a drop of 5% tincture of iodine. Shake solution, and if reaction is positive a persistent golden-yellow colour is produced. Reaction positive in the first week, increasing in intensity until disease reaches its height and then decreasing, becoming negative before temperature becomes normal. Also invariably positive in pulmonary tuberculosis with cavity formation, very frequently in second stage and occasionally in first stage. Often positive during height of pneumonia and measles, and always negative in malaria and acute rheumatism. Of greater diagnostic value than the diazo-reaction, owing to earlier appearance, greater constancy and longer duration.—*Lancet*, i/1924, 245.

Russo's Test for Suspected Typhoid Fever. Four drops of a 0.1% aqueous methylene blue solution to be added to 4 ml. or 5 ml. of urine. Green colouration stated to be positive—blue, negative.

Paratyphoid Fever, in the true sense, is an infection with paratyphoid A and B bacilli. The disease is similar to typhoid though generally running a milder course. Intestinal ulcers are identical with those of typhoid. Cases of mixed infection are not rare.

Paratyphoid A and paratyphoid B are morphologically like the typhoid bacillus and are actively motile but ferment glucose with production of acid and gas.

B. paratyphosus A produces less gas in glucose media than B with A, milk remains acid for a fortnight and then becomes alkaline after a transient acidity; and though A changes neutral red to yellow, the red colour tends to return after 3 weeks or so while with B the yellow colour is permanent. That is to say, in its reactions A is more closely allied to the typhoid bacillus than B.

B. paratyphosus B, however, ferments xylose and blackens lead acetate medium, while A does not, and B is regarded as more closely allied to the Gaertner group than A.—Hewlett and McIntosh.

***B. paratyphoid B*.** Differentiation of *B. aertrycke* from, also a sub-division of the aertrycke organisms.—H. Schütze, *Lancet*, i/1920, 93.

Study of 63 strains belonging to *paratyphosus B* group; all produce acid and gas in arabinose, dulcitol and xylose, and a

but 5 produce transient acidity in inosite; all ferment trehalose and blacken lead acetate medium, differentiating them from organisms of *enteritidis* and *suipestifer* groups. Capable of division into two sharply-cut groups; 33 strains, containing all strains isolated from paratyphoid fever in man, and nearly all *paratyphosus B* strains of porcine origin—suggested name for this group, "*Schottmüller Type*"; the other group of 27 strains all isolated from food-poisoning outbreaks, together with all strains of rodent origin—as all in this group agree in ability to absorb homologous agglutinins from *aertrycke* "mutton" serum, the suggested name is "*Aertrycke Type*." Both groups more closely allied to each other than to *B. enteritidis* type.—*Brit. med. J. Epit.*, i/1924, 44.

Cole and Onslow's Tryptic Broth. A broth using casein (lait-proto No. 6, for bacteriological purposes), digesting this with fresh pancreatic extract and adjusting the reaction by making the hydrogen ion concentration about pH 7.35. This reaction is very near that of blood serum and also near the optimum pH for the growth of most pathogenic organisms.

The broth gives luxuriant growth with the colon-typhoid group, also with *B. diphtheriæ* and the *meningococcus*. It is most useful for testing for indole formation owing to its rich content of free tryptophane. When diluted with its own volume of 0.5% sodium chloride it is an excellent medium for detection of acid and gas formation. It is also good for making agar media.

Phenol red is employed in the medium to differentiate *B. typhosus* and *B. paratyphosus A* and *B* by a method based on the pH reached in growth of the organisms. For the separation of T from A, formation of gas in glucose and the rapid fermentation of dulcitate by A and not by T are relied on.

Phenol red is useful as indicator. Does not appear to inhibit growth and is more sensitive than litmus. Lemon-yellow in acid solution and red or magenta in alkaline. Solution of strength 0.04% is added to the glucose tryptic broth and a dulcitate medium in proportion of 4% of the solution.

Following are the critical points of difference.—

Organism	Solution "G," Glucose Tryptic Broth and Phenol red	Solution "D," Dulcitate Tryptic Broth and Phenol red	Glucose fermentation tubes
<i>B. typhosus</i>	Yellow	Red or pink	Acid
<i>B. paratyphosus A</i>	Yellow	Yellow	Acid and gas
<i>B. paratyphosus B</i>	Red or pink	Variable	Acid and gas

—S. W. Cole and H. Onslow, *Lancet*, ii/1916, 9, 1011.

B. paratyphosus C culturally resembles B but does not ferment inosite and is inagglutinable with typhoid, paratyphoid A, paratyphoid B, and Gaertner sera of high titre. Andrews and Neave find that C belongs serologically to the *B. suipestifer* series and has affinities with *paratyphosus B*. It differs culturally from other strains of *B. suipestifer* in fermenting arabinose.—Hewlett and McIntosh.

See also *Food Poisoning and Hog Cholera*, this volume.

Anti-typhoid-paratyphoid Vaccine (B.P. '32). A sterile suspension of the micro-organisms *B. typhosus*, *B. paratyphosus A*, and *B. paratyphosus B*, which have been killed. It contains in 1 ml. 1000 million *B. typhosus*, 500 million *B. paratyphosus A* and 500 million *B. paratyphosus B*.

For further details see Vol. I.

Typhoid Carriers. In Gt. Britain the fall in incidence of enteric fever due to abolition of gross contamination of water supplies, has, if possible, enhanced the importance of chronic carriers who are now the chief causes of epidemic outbreaks. In paratyphoid B infections especially, the incidence of *temporary* carriers in *convalescence* is high and due precautions should be taken during the convalescent period. Most of those who continue to excrete bacilli for 6 months after the acute attack will continue to do so, and in those who still excrete after a year the carrier state becomes chronic or permanent. The more dangerous (because more elusive) carrier is the chronic carrier who has had no known attack or whose carrier state is intermittent. The two main routes are fæcal and urinary. The chronic fæcal carrier is usually a married woman of 30 years of age or upwards. Female chronic carriers exceed male in the proportion of 4 or 5 to one. Children rarely become carriers but are important agents in dissemination, as attacks are so often mild and atypical. Fæcal carriers are by far the most numerous and may be subdivided into the biliary carrier and the rare true intestinal carrier, but urinary carriers (the nidus of infection being most commonly the kidney or kidney pelvis) are more dangerous owing to greater opportunities for spreading infection and greater concentration of organisms in the urine. General anti-enteric inoculation is not practicable, but in closed communities it is practicable and highly desirable, though as protection tends to wane after a year it must be repeated. In addition to bacteriological evidence of freedom from infection before discharge of a case from hospital, examination should be made again 6 to 12 months later. In the treatment of the chronic fæcal carrier, chemotherapy, physiotherapy, vaccine therapy and administration of *B. acidophilus* are all ineffective, but where the gall-bladder is the site of infection cholecystectomy has been successful in terminating the carrier state in 75% of cases, and offers the best chance of success.—C. H. Browning and co-workers, *Spec. Rep. Ser. med. Res. Coun., Lond., No. 179, 1933; Lancet, i/1933, 535.*

The enteric fevers in Great Britain have diminished, are diminishing, and should continue to diminish. Deaths and incidence have shifted from the large towns to the smaller towns and rural districts. Epidemic influence is chiefly due to water and milk in the small towns and rural districts, and to specifically infected foods in the large towns.—N. M. Goodman, *Lancet, ii/1933, 771.*

The typhoid bacillus is excreted in the urine in the later stages of typhoid fever, and it may exist in the urine without causing symptoms. Such carriers are a great source of danger to others.

A typhoid-carrier survey of 1076 healthy dairy employees in Alabama yielded 55 carriers of typhoid and paratyphoid bacilli, i.e., 5.1%.—S. W. Welch and co-workers.—*J. Amer. med. Ass., ii/1925, 1038.*

For typhoid and paratyphoid organisms in water see *Water Analysis, this Volume.*

Typhus Fever. The disease is characterised by a rapid onset, the development of a mottled rash on the trunk and limbs about the fourth day, and complete delirium. The disease lasts about 10 to 14 days and usually ends by a sudden crisis. Catarrhal symptoms are present and even broncho-pneumonia. The virus of typhus fever is present in the blood, which is infective from the onset and continues so until the day after the temperature becomes normal.

In addition to the characteristic and severe disease, milder forms occur in certain areas and have received local names: such are *tabardillo* of Mexico and S. America, *Brill's disease* of the U.S., *Manchurian fever* of S. Manchuria, *scrub typhus* of Malaya, *Marseilles typhus* and *Toulon disease*.—Hewlett and McIntosh.

See also *Mediterranean Fever* and *Rocky Mountain Spotted Fever.*

Bacteriology. The organism now generally considered responsible for the disease is *Rickettsia prowazeki*, first described

by da Rocha-Lima in 1916. The organisms stain a reddish-purple with Giemsa, are very small, of short elliptic or olive shape, often in pairs and are surrounded by a paler staining substance; occasional very short and very long forms—up to 1.5 to 2 μ —may be seen. Da Rocha-Lima observed this organism in the lice taken from 95% of typhus patients.—Topley and Wilson.

Transmission. The disease is spread by the body-louse, which becomes infected by ingesting the blood of a patient.

Distribution. The latest notification of typhus fever in England and Wales was received in 1929. A few cases are reported each year in the I.F.S., but their number is decreasing. In Europe typhus fever remains practically confined to the Eastern States, including the Balkans. Brill's disease is endemic in the south-eastern parts of the U.S.A. and in Central and South America, and a similar form has been described in Australia.—*Rep. med. Offr Minist. Hlth, Lond.*, 1933, 48.

Typhus fever: its prevalence. A review of typhus fever in the world. Figures for South Africa, Algeria, Chili, U.S.A., Rumania, and Soviet Russia.—*Bull. Off. Int. Hyg. publ.*, per *Lancet*, ii/1934, 940.

Diagnosis. Weil-Felix Reaction is distinctive. The X2 and X19 strains of *B. proteus* are agglutinated by the serum of typhus cases. It is similar to the Widal reaction.—*J. R. Army med. Cps*, 1923, 210.

A positive reaction at 1:25 during the first week of the disease may be considered as a presumptive positive, though about 7% to 9% of persons not suffering from typhus may react at this titre. As a rule the titre rises rapidly so that a positive diagnosis, 1:50 or higher, can generally be made by the 8th day. The reaction has been employed on a large scale and has been found remarkably valuable.—Topley and Wilson.

The reaction must be interpreted with caution. Conclusive in very high titres, above 1:1000; titres of 1:100 very suggestive, but 1:50 only indicates possibility of typhus. Unusual for reaction to be so pronounced in diseases other than typhus as to be regarded as positive, but it is occasionally positive in scarlet fever and small-pox, and most likely to be so in paratyphoid B fever—a case in point. Rise of titre during disease a strong argument in favour of typhus. Author recommends examination by both Weil-Felix and Widal Tests, also, in sporadic cases, by Nicolle's method (injection of 0.25 ml. of serum into peritoneum of guinea-pig or monkey). In positive cases, after incubation period of 10 days, fever sets in lasting 6 to 12 days. Negative result has no significance.—*Brit. med. J. Epit.*, i/1924, 36.

The strength of the reaction does not correspond to the gravity of the disease. Mild cases may give strong reactions, but a high reading was also obtained in a patient shortly before death.—E. H. R. Altounyan, *Lancet*, i/1924, 76.

Treatment. Support the heart by digitalis or strophanthus, large injections of camphorated oil, injections of rum and injections of adrenaline if syncopal attacks occur. Avoid antipyretic drugs. Optochin, 1 g. to 2.5 g., daily *per os*, has been advised by German physicians to be taken so long as patient can swallow. When coma supervenes, to be given in oil hypodermically. Said to cut short the fever and lessen mortality.—*Brit. med. J.*, i/1916, 621.

Notes on about 1800 cases in the Serbia epidemic, 1915. Washing the mouth out with **permanganate** or, in preference, **hydrogen peroxide** obviated parotitis, otitis, etc. Ice to the head.—T. Gwynne Maitland, *Brit. med. J.*, ii/1915, 283.

2000 cases in a German prison camp. Camphorated oil hypodermically, but not found good; much abscess formation. **Morphine** is a sheet anchor. Expectant and symptomatic treatment best.—P. C. T. Davy and A. J. Brown, *Brit. med. J.*, ii/1915, 737.

Typhus fever epidemic among Greek refugees—treatment described.—Sir P. Hehir, *Lancet*, ii/1923, 153, 209, 264.

Prophylaxis. A person unprotected by a previous attack exposing himself to a typhus patient in a close room runs risk, even though there are no lice present. Good ventilation essential.—J. W. Allan, *Brit. med. J.*, ii/1915, 841.

Kerosene or equal parts of kerosene and soft paraffin for anointing the body is an efficient insecticide.—R. O. Moon, *Lancet*, i/1916, 1069, 1111, 1157.

S. African typhus among natives. Hot air deverminisation apparatus working for 20 minutes at 75° advised. Naphthalene 1, in nut oil 8, is an efficient insecticide for disinfecting head and body while clothes are going through the machine; it kills lice and nits on hair and body.—H. F. Sheldon, *Lancet*, ii/1922, 1075.

Prophylactic inoculation. A serum made by passage of the virus through the monkey is preventive.—S. Kusama, *Lancet*, ii/1921, 386.

Undulant Fever, syn. Malta Fever. (Note.—Mediterranean fever, *q.v.*, is *not* synonymous).

The fever is characterised by long irregular pyrexia, with frequent relapses. There is profuse perspiration, pains and sometimes swellings in the joints, occasionally orchitis. Constipation is usually very marked. Incubation period 6 to 9 days. Temperature may be 106°, fatal 110°F. The mortality rate is about 2%.

In 1886, Bruce found *Micrococcus melitensis* in the spleen of fatal cases of Malta fever, and by inoculating monkeys proved it to be the cause, but it was not until 1905 that Zammit was able to indicate that goat's milk was the main source of infection. Following the stoppage of the supply of goat's milk the disease was practically eradicated among the troops, and the killing off of infected goats has since greatly reduced the incidence in the civilian population.

M. melitensis is actually a bacillus and not a coccus, and the name now adopted is *Brucella melitensis*, the "abortus" organism now being regarded as a variety (*Brucella melitensis*, var. *abortus*)—per *Prescriber*, 1929, 303.

Br. abortus was first isolated by Bang in 1897 from cow suffering from infectious abortion.

Morphology. *Br. melitensis* and *Br. abortus* have a fairly close resemblance morphologically. The bacilli are short and slender, the axis is straight; the ends are rounded; the sides may be parallel or convex outwards. In length they vary from about 0.6 to 1.5 μ and in breadth from 0.5 to 0.7 μ . The short form may appear as oval cocci or as diplococci. As a rule they are arranged in pairs end-to-end, or in small groups; sometimes short chains of 4 to 6 members may be seen. Owing to the frequent coccoid appearance their bacillary nature may be in doubt, but in size they are smaller than any of the gram-negative cocci.—Topley and Wilson.

Incidence. The incidence in this country is not known, as the disease is not notifiable, but it is becoming better known and the improvement in diagnosis is reflected in the increasing number of cases which have come to the notice of the Ministry of Health: in 1928, 5; 1929, 17; 1930, 28; 1931, 40; 1932, 57. Undulant fever should not be regarded as a last resort in diagnosis but as a definite possibility in all cases of irregular or prolonged fever. Details of cases asked for, for the records of the Ministry of Health and the Agricultural Research Council.—Sir W. Dalrymple-Champneys, *Lancet*, i/1934, 95.

Of 1331 sera examined at Manchester for the *Brucella* and enteric groups between January 1929 and November 1932, 28 agglutinated *Br. abortus* only. Evidence is accumulating to show that latent and subclinical infection is not uncommon and the low incidence must depend on the relative insusceptibility of the human population.—E. Wade, *Lancet*, i/1933, 1342.

Since 20% to 40% of the mixed milk supplies in towns not practising pasteurisation contain living *abortus* bacilli, and a high proportion of herds are infected, it is often asked why undulant fever is not more common in this country than it appears to be. The answer is that, as with the tubercle bacillus

latent infections with *Br. abortus* are common. Of 100 slaughterers examined at Liverpool, 12 had an agglutination titre of 1:40 or over to *Br. abortus*, while of 100 control males of the same age-groups only 2 reacted at this titre.—*Lancet*, ii/1932, 581.

See also H. Harrison and G. S. Wilson, *Lancet*, ii/1928, 1340. The more the disease has been looked for in the U.S.A. the more it has been found.—*Lancet*, ii/1928, 1349.

Diagnosis. In the early stages of the disease in man, blood culture is the most satisfactory method of diagnosis: it is positive in about 80% of cases from the second day onwards.

Citrate 10 ml. of blood, centrifuge with normal saline twice and take up organisms and red cells with pipette; 1 ml. added to tube of agar at 40° and poured into petri dish; several plates made and incubated at 37°; organisms picked out from 2nd to 6th day.—*J. trop. Med. (Hyg.)*, 1924, 80.

Blood culture a valuable method of diagnosis. The best culture medium is 1% glucose broth and incubation prolonged in an atmosphere of 10% carbon dioxide.—G. S. Wilson, *Brit. med. J.* i/1934, 301.

Br. abortus cultivated from human faeces—method described.—H. L. Amoss and M. A. Poston, *J. Amer. med. Ass.*, ii/1929, 170.

Agglutination Test.—In the blood of normal persons agglutinins may be present for *Br. melitensis*, sometimes up to a titre of 1:50, occasionally to 1:100. In patients suffering from Malta fever, specific agglutinins appear about the 10th or 12th day after the commencement of the fever; the titre rises till it attains a point varying between about 1:100 and 1:3000. Provided that the precautions are taken of using known agglutinable strains of both serological types, that no reaction is considered possible in a serum dilution of less than 1:50, and that in all doubtful cases the reaction is repeated in 5 days' time to ascertain if the titre is rising, there is little chance of error.—Topley and Wilson.

At the Public Health Laboratory, Manchester, during 1927, 998 Wassermann sera, and 42 Widal sera, were examined. By examining the former it was hoped to gain some idea of the normal titre to *Br. abortus*, and by examining the latter to detect cases of abortus fever amongst the numerous cases of undiagnosed pyrexia from which these sera were derived. Of the Wassermann sera 5.5% agglutinated *Br. abortus* to a titre of 1:10 or higher, and of the Widal sera (all negative to organisms of the typhoid-paratyphoid group) 26.2% agglutinated *Br. abortus*. The average titre of the Wassermann sera was 1:64 and of the Widal sera 1:336. The evidence suggests that blood cultures and agglutinin tests should be made on all cases of undiagnosed maladies.—H. Harrison and G. S. Wilson, *Lancet*, ii/1928, 1338.

Dr. M. Kristensen of Copenhagen examined 1177 Widal sera and found that 89 of them agglutinated *Br. abortus* to 1:100 or higher. Blood cultures were made from 20 of these patients and in 13 of them an organism indistinguishable from *Br. abortus* was isolated.—*ibid.*

Intradermal Reaction.—Burnet's intradermal "**Melitene**" Test consists in injection of 0.5 ml. of a killed broth-culture containing 500,000 organisms. If positive, a red oedematous area occurs at site of injection persisting for several days.—*Prescriber*, 1929, 306.

Intradermal test with phenolised suspension of heat-killed bacteria as an aid to diagnosis. Results should be read 96 hours after injection. Positive results may lead to definite diagnosis in absence of positive agglutination test. Results same with *Br. abortus* and *Br. melitensis*.—H. C. Yeckel and O. D. Chapman, *J. Amer. med. Ass.*, i/1933, 1858.

Treatment. *Brucella melitensis* vaccines containing 2000 million *Br. melitensis* organisms per ml. are available (see N.N.R. 1935) for use in the treatment of undulant fever. The vaccine is given subcutaneously at intervals of from 3 to 10 days in doses of 0.25 ml., 0.5 ml., and 1 ml.

Fever kept under by physical measures. Vaccines useless, but eusol double strength intravenously in 50 ml. doses or acriflavine intravenously in doses of 0.1 g. to 0.4 g. are both stated to have given good results.—*Prescriber*, 1929, 307.

Goats vaccinated intravenously with *Br. abortus* in massive doses protected from subsequent infection with a virulent *Br. melitensis* strain and fail to pass that organism in milk.—*J. trop. Med. (Hyg.)*, 1924, 195.

Value of live vaccine of *Br. abortus* for protecting inoculated animals against infection challenged.—Sir John McFadyean, *J. comp. Path.*, March, 1933, 50.

Weil's Disease. In the first stage, lasting 6 or 7 days, there is high fever, conjunctival congestion, muscular pains and albuminuria; in the second stage, lasting from the 7th to the 13th day jaundice appears, with a tendency to hæmorrhage, and death may occur; the convalescent stage is marked by general subsidence of the jaundice and other symptoms, but may be interrupted by a secondary fever.

Leptospira icterohæmorrhagiæ, the causal organism, is 6 to $10\text{ }\mu$ in length, $0\cdot25\text{ }\mu$ in thickness, and contains a number of perfectly regular, closely-wound spirals about $0\cdot5\text{ }\mu$ long; the spirals become closer near the extremities. A most characteristic feature is the sharp, tapering, hooked ends, giving the organism a resemblance to the letter C or S.

During the first week of the disease the spirochætes can generally be demonstrated in the blood by guinea-pig injection and by microscopical examination. After the 7th to 9th day they leave the blood and appear in the urine, in which during the 3rd and 4th weeks they can be found microscopically by dark-ground illumination (the spirochætes in the urine are often atypical in shape and may be granular and degenerated).—Topley and Wilson.

Transmission. The evidence indicates that infection takes place by contamination of the abraded skin or the conjunctiva with water contaminated with rat's urine.

In the course of a few years wild rats have spread the infection throughout the whole world, spirochætes being found constantly in their kidneys and urine. 40% of rats in Freiburg are infected, and in Germany it is believed that the principal source of human infection is from baths, where the water has been contaminated from the urine of infected brown rats. It appears probable that tame rats, though not hitherto regarded as potential carriers, may also be infected. Rats' saliva usually contains spirochætes and men may be infected by handling them.—P. Uhlenhuth and E. Zimmerman, per *Brit. med. J.*, ii/1933: 1083.

A case of Weil's disease contracted by the "whip" of a pack of foxhounds following p.m. of puppies which had died from "yellows" (a leptospiral disease of dogs). The association of human with canine jaundice may not be so uncommon as the recorded cases suggest. The virus is easily transmissible by skin contact.—C. J. M. Lawrence and C. C. Okell, *Lancet*, ii/1929, 328.

Incidence. A widespread and hitherto unrecognised focus of Weil's disease affecting the sewer labourers of London has been demonstrated, and its existence for at least $12\frac{1}{2}$ years conclusively proved, many cases having been diagnosed as catarrhal jaundice. A serological and clinical examination of sewer workers should be undertaken to determine the real extent of the disease, and prophylactic leptospiral vaccines might prove valuable.—N. H. Fairley, *Brit. med. J.*, ii/1933: 13.

Details of a case occurring in a female Post Office employee.—W. C. Willoughby and A. G. Shera, *Brit. med. J.*, ii/1934, 14.

Nineteen cases reported in Aberdeen, in fifteen of which clinical diagnosis was confirmed by bacteriological or serological tests. Thirteen of the patients were employed in the handling and cleaning of fish. The premises where fish are cleaned and prepared for distribution are often unsatisfactory, unhygienic, and infested with rats, and samples of water taken from floor-washings and tubs caused typical ictero-hæmorrhagial infection in guinea-pigs, the organism being easily demonstrable. These findings show that the workers among fish must be included in the occupational groups especially liable to Weil's disease.—L. S. Davidson and co-workers, *Brit. med. J.*, ii/1934, 1137.

Account of an outbreak in Queensland, with 136 cases and 7 deaths. The outbreak occurred in a low-lying area with heavy rainfall, devoted to the growth

of sugar cane. The cane-cutters (mostly Italians) work bare-footed in the cane-fields, which are heavily infested with rats. Description of preventive measures adopted.—J. G. Drew, *Brit. med. J.*, ii/1934, 1142.

In Japan the disease remains prevalent, the total cases in 1933 being 1636, with a mortality of 4.6%, though in one province the mortality over six years varied from 16.9% to 29.9%.—*Brit. med. J.*, ii/1934, 1155.

L. icterohæmorrhagiæ discovered in wild rats caught in slaughter house at Warsaw—4 out of 42 infected. Two strains possessed very high virulence for guinea-pigs. From experiments, the isolated leptospira concluded to be identical with *L. icterohæmorrhagiæ*.—Ludwig Anigstein, *J. trop. Med. (Hyg.)*, 1923, 81.

L. icterohæmorrhagiæ found in the urine of a rat caught in a wet seam in a North of England coal mine.—H. A. Cookson, *Lancet*, ii/1935, 192.

Diagnosis. Agglutination Test. This is carried out by allowing varying concentrations of the patient's serum to interact for 2 hours at 32° with an equal volume of a young culture of *L. icterohæmorrhagiæ*. Drops from these dilutions are then examined by dark-ground illumination. If formolised cultures are used, lysis of the leptospira does not occur. The technique of the reaction is described by W. Schüffner, *Trans. R. Soc. trop. Med. Hyg.*, 1934, 7.

Positive agglutination reaction may be expected on the sixth day of the disease and reaches its maximum on the twentieth.

Adhesion Test. About 20 c.mm. of each of (a) patient's serum, (b) young broth culture of *L. icterohæmorrhagiæ*, (c) saline suspension of young culture of *B. coli* or similar organism and (d) a five-fold dilution of fresh guinea-pig's serum in saline are mixed in a small incubation tube and incubated at 37° for half an hour. A control tube containing normal serum in place of the patient's serum is similarly treated. A drop of the fluid is examined under a cover slip with dark-field illumination. In a positive reaction the bacteria will be seen to be firmly adherent to the leptospira although not all the leptospira will be affected in this way unless the serum is of very high titre. In a negative reaction the leptospira are seen to be swimming freely unimpeded by the bacteria. At least twenty leptospira should be observed before a negative result is recorded.—H. D. Brown, *Lancet*, i/1935, 411. Culture medium used is composed of distilled water 3 ml., Lemco broth 0.5 ml., inactivated rabbit's serum 0.25 ml. Culture incubated at 32° for 6 days. Better to use a strain that has lost its pathogenicity.—*ibid.*

Treatment. Specific therapy, both in the form of convalescent serum and antileptospiral serum is available.

Whooping Cough. Bordet's Bacillus. A cocco-bacillus, non-motile, gram-negative, staining feebly, regarded as causative of whooping cough, has been isolated. Cultures of the organism were found to be specifically agglutinated by the serum of children suffering from the disease. Agglutinating reaction not strong.

Resembles *B. influenzae* (Pfeiffer) and grows somewhat scantily on blood agar. The following medium permits of isolation from sputum. Potato 500 g., 4% glycerin solution 1000 ml.; autoclave and pour off excess fluid. Emulsify potato in normal saline 1500 ml. and add agar 3% to 4%. For use, mix with equal quantity of defibrinated blood.

Frequency of finding Bordet's bacillus diminishes markedly after end of the 4th week of the spasmodic phase.—*Brit. med. J.*, ii/1926, 663.

The bacillus isolated in cases examined within the first week. A pearl-like colony developed after 3 days' incubation. Easier and more exact than bacterial diagnosis of diphtheria.—H. Sugare and J. W. McLeod, *Lancet*, ii/1929, 167.

The nature of the culture medium is of great importance in regard to antigenic capacity. Bacilli grown on rich blood medium differ antigenically from those grown without blood, but even when grown in blood agar the bacilli degenerate in immunising power.

Analysis of the antigenic properties of 32 strains of *B. pertussis* showed that they fell into four well-marked groups termed Phases I, II, III and IV. Freshly isolated strains were toxic to guinea-pigs (Phase I), stock laboratory

strains were non-toxic and were Phases III and IV. A culture from a single colony can produce in turn all the antigens characteristic of the four phases, and in culture the bacilli tend to change to Phases III and IV. This change can be delayed by incorporating sufficient fresh blood in the culture medium. An efficient prophylactic vaccine can be made only from bacilli in the pathogenic Phase I.—P. H. Leslie and A. D. Gardner, *J. Hyg., Camb.*, 1931, 423.

Yaws, syn. Frambœsia. A contagious inoculable disease characterised by an indefinite incubation period followed by fever, by rheumatic pains, and by the appearance of papules which develop into a fungating, encrusted, granulomatous eruption.

An organism found in the lesions of yaws has been named both *Spirochaeta pallidula* and *Treponema pertenue*.—Manson.

Epidemiology and morbidity of yaws, with special reference to fat metabolism. Low diet values, scarcity of animal protein, absence of milk, fat, calcium and vitamin A, are factors.—J. O. Shircore, *Lancet*, i/1930, 960.

Some 56,000 cases are being treated each year in Nigeria.—W. B. Johnson, *Brit. med. J.*, ii/1932, 288.

FRAMBŒSIA in Ceylon. Potassium iodide in large doses best routine treatment. Atoxyl, sodium cacodylate, and quinine cacodylate also useful.

Novarsenobenzol has a rapid and remarkable curative action in every stage of the disease.—Manson.

Yellow Fever. Yellow fever resembles Weil's disease, but the symptoms are more severe and hæmorrhages into the stomach and intestine cause black vomit and melæna. Has a very high mortality rate.

Yellow fever no longer exists in North America and has been largely suppressed in Central and South America; it is now mainly prevalent in West Africa.

Noguchi thought the disease to be due to *Leptospira icteroides* but it is probably caused by a virus which will pass the pores of V and N Berkefeld filters but not W.—*Brit. med. J.*, i/1928, 72.

For details of Noguchi's work and a description of *L. icteroides* see 19th Edn., Vol. II.

Transmission. The Americans, Reed, Carroll, Agramon and Lazear established that yellow fever is transmitted by *Aedes ægypti* (syn. *Stegomyia calopus*, *S. fasciata*). The virus can be transported from one place to another. For its development requires a temperature of over 75°F. It ceases to spread below 75°. Usually it is a sea-coast disease. The mosquito is the intermediary but it is not transferable by recently infected mosquitoes. The parallelism between the ætiology of yellow fever and malaria is very complete.—Manson.

Aedes univittatus (Sugeus) and *Tæniorrhynchus africanus* (both common domestic mosquitoes) as potential carriers in W. Africa.—W. B. Johnson, *Brit. med. J.*, ii/1932, 285.

Other species of mosquito than *Aedes ægypti* may carry the disease—campaign in W. Africa should be directed against all mosquitoes indiscriminately. E. Hindle, *Brit. med. J.*, ii/1930, 1053.

An account of a unique epidemic in South America during 1932 is given by F. L. Soper et al., *Amer. J. Hyg.*, xviii, 555. In one district in Brazil, *A. ægypti* could not be found, but another species of mosquito, *Aedes scapularis*, was incriminated as vector.

The Brazilian epidemic is a grave warning that in certain circumstances a potential but usually inefficient vector can spread yellow fever.—S. F. Dudley, *J. trop. Med. (Hyg.)*, 1934, 273.

For a discussion of the ecology of mosquito-borne disease with reference to possibility of spread of yellow fever to Asia, see S. F. Dudley, *ibid.*

Yellow fever ætiology. Incubation period longer than hitherto supposed. Cultural problems discussed.—Max. H. Kuczynski and B. Hohenadel, *Lancet*, i/1930, 180.

Contamination with infected blood the usual method of transmission. Infected human blood is highly infectious in the early stages and may carry the disease by percutaneous route since the virus is able to pass through the intact skin.—E. Hindle, *Lancet*, ii/1930, 835.

The Dutch Government has made it a punishable offence to import for scientific purposes yellow fever virus into the Dutch East Indies, and the Government of India has taken similar steps.—*Brit. med. J.*, ii/1932, 325.

Immunisation. It is possible to show if a person is immune to yellow fever by injecting his blood serum together with yellow fever virus into a specially prepared mouse. If the subject is immune the mouse does not die.—W. A. Sawyer and W. Lloyd, *J. exp. Med.*, 1931, 539.

The "protection test" developed by workers in W. Africa shows that the injection of a small quantity of serum from a patient who has recovered from the disease protects white mice from a simultaneous injection of yellow fever virus. The principle consists of an intraperitoneal injection of the serum to be tested and the virus, and at the same time a mild irritant (starch solution) is injected into the brain to fix virus entering the circulation. The test has profoundly modified views on the epidemiology of the disease as it has shown that the immunity conveyed by an attack is usually lifelong. Though it may be serious, the disease in Africans is usually a trivial illness occurring in infancy, and hundreds of cases must occur which are not recognised—which would account for the occurrence of the disease among Europeans in places widely separated where there is no evidence of a native epidemic.—W. B. Johnson, *Brit. med. J.*, ii/1932, 285.

Passive immunity from injection of immune serum alone disappears in one or two weeks; more prolonged immunity results from subcutaneous or intraperitoneal inoculation of a mixture of virus and immune serum.—G. M. Findlay and E. Hindle, *Brit. med. J.*, i/1931, 740.

By passage through mice yellow fever virus loses its virulence for monkeys.—M. Theiler, *Ann. trop. Med. Parasit.*, 1930, 249.

After 100 or more passages through mice, the virus, although of low virulence, is still capable of producing yellow fever in man and should be further attenuated or mixed with a potent immune serum. After a single injection of a dried mixture of living mouse virus and human immune serum, immunity of 15 persons inoculated rose to an extent comparable to that following a natural attack.—W. A. Sawyer, S. F. Kitchen and W. Lloyd, *J. exp. Med.*, 1932, 945.

In this country, up to the end of 1933, 200 persons were immunised by injection of neurotropic mouse-fixed yellow fever virus and human yellow fever immune serum. Of these, about 50% developed febrile reactions lasting 24 to 48 hours, but in only a very small number was the reaction severe. Immune bodies appeared in the blood stream 7 to 8 days after inoculation and attained maximum titre in 3 to 4 weeks. Protective immune bodies still detected up to 16 months and probably longer. Success so far demonstrated in laboratory workers, in whom there was complete absence of the accidental infections, at one time so common.—G. W. M. Findlay, *Brit. med. J.*, i/1934, 260.

Encouraging prophylaxis obtained with a phenol-glycerin vaccine prepared from the liver and spleen of infected monkeys.—E. Hindle, *Brit. med. J.*, i/1928, 977.

Vaccine prepared from a strain of virus after intracerebral passage through mice does not produce fatal disease in monkeys but produced immunity after either subcutaneous or intraperitoneal injection. Killed monkey-virus vaccine did not produce immunity in man but antibodies found in serum of patients after inoculation with living mouse-passage virus obtained from brains of infected mice.—A. W. Sellards and J. Laigret, *Brit. med. J.*, i/1933, 82.

Mouse protection test gives no support to suggestion that an attack of dengue protects against yellow fever, since several investigators have found that the blood serum from a recovered case of dengue contains no immune-body to yellow fever.—C. M. Findlay, *Trans. R. Soc. trop. Med. Hyg.*, 1934, 437.

CULTURE MEDIA FOR BACTERIOLOGICAL INVESTIGATION

1. **Bile Salt Dextrose Broth** [MacConkey's Medium (Double Strength for *B. coli communis*)]. Triturate 40 g. of peptone into a cream with water and add it to 1000 ml. of hot water containing 10 g. of sodium taurocholate. Boil the liquid for 30 minutes, cool, and add 10 g. of dextrose. Sterilise by steaming at 100° for 20 minutes, adjust to pH 7·4, filter through filter paper into a sterile flask, add sterile litmus solution to colour the medium to a deep purple. Place 10 ml. quantities into tubes containing small gas tubes and plug. Sterilise by steaming at 100° for 20 minutes.

(The medium is sometimes prepared with neutral red instead of litmus.)

2. **Blood Agar** [Citrate Blood Agar (Guy's)]. Kill a small rabbit with chloroform vapour, open up the thoracic cavity and pericardium, maintaining the strictest aseptic precautions throughout the operation. Insert a sterile plugged pipette into the heart. Apply suction to the plugged end and fill with blood. Transfer the blood to a small sterile flask containing sterile glass beads and 5 ml. of a sterile 10% solution of sodium citrate in normal saline. Agitate thoroughly and set aside for 2 hours. Warm several tubes of sterile nutrient agar to 42° to melt and transfer aseptically 1 ml. of the blood to each plug, and rotate the tubes so as to diffuse the blood evenly throughout the medium. Slope the tubes and allow to cool. Incubate at 37° and reject any contaminated ones.

3. **Blood Serum Medium.** Place freshly collected ox or sheep blood in a sterile cylinder and allow to stand for about 15 minutes until the blood has coagulated. Separate the clot from the sides of the vessel using a sterile glass rod, and place the cylinder in an ice chest for 24 hours.

Pipette off the serum in 5 ml. quantities into sterile tubes, and plug. Heat to 56° for 30 minutes on each of two successive days. On the third day heat the tubes in a sloping position in a serum inspissator to about 72° so as to form a transparent jelly-like coagulum (a higher temperature will give a turbid jelly). Incubate at 37° for 48 hours and reject those showing growth. Store the remainder in a cool place.

4. **Blood Serum** (Loeffler). Prepare nutrient broth using a veal extract instead of beef. Dissolve 1% dextrose in the broth. Add 300 ml. of clear blood serum (prepared as for Blood Serum Medium) to every 100 ml. of broth. Tube and complete as for Blood Serum Medium.

5. **Egg Medium** (Dorset). Wash twelve fresh eggs externally with water, then with solution of formaldehyde and finally in methylated spirit. Allow to dry. Break the eggs into a sterile graduated cylinder and measure the total volume of mixed whites and yolks. Add 1 volume of sterilised normal saline to 3 volumes of the mixed eggs. Transfer to a large, wide-mouthed, stoppered bottle, previously sterilised. Add sterile glass beads and shake thoroughly in a mechanical shaker for 30 minutes. Filter through muslin. Add, if required, a few drops of alcoholic solution of magenta. Tube in quantities of 10 ml. Heat the tubes in a sloping position in a serum inspissator at 75° to 80° for one hour. Incubate at 37° for 48 hours and reject any contaminated tubes. Cap the remainder with sterile rubber caps and store.

6. **Glucose (Dextrose) Broth.** Incorporate 20 g. of dextrose in 1000 ml. during the preparation of nutrient broth. Sterilisation should be carried out by steaming at 100° for 20 minutes on three successive days.

7. **Glucose Agar Broth.** Rub 20 g. of powdered agar into a smooth paste with 750 ml. of nutrient broth. Heat on a water-bath and pass steam through the medium until the agar is dissolved. Incorporate 20 g. of dextrose and warm gently until dissolved. Adjust to 1 litre with hot nutrient broth. Sterilise by steaming at 100° for 30 minutes on each of three successive days.

8. **Glycerin Blood Agar.**—Prepare blood serum as described under Blood Serum Medium and place in sterile tubes. Add 5% *v/v* of glycerin and proceed as for Blood Serum Medium.

Different percentages of glycerin are used for special purposes, but 5% is usually employed.

9. **Glycerin Broth.** Nutrient broth containing 6% *v/v* of glycerin.

10. Lactose-Bile-salt-Agar Medium (MacConkey's Neutral Red Bile Salt Agar).—Rub 20 g. of peptone into a paste with 150 ml. of distilled water. Add 10 g. of lactose and 5 g. of sodium taurocholate dissolved in 500 ml. of distilled water and bring the peptone into solution with gentle heat. Rub 20 g. of powdered agar into a smooth paste with some of the solution and incorporate the remainder. Heat on a water-bath and bubble steam through until the agar is dissolved; then adjust to 1 litre with boiling distilled water. Adjust the reaction of the medium to pH 7.0. Thoroughly whip the whites of two eggs and add to the medium. Steam at 100° for about 1 hour to coagulate the egg albumen and filter (using a hot-water funnel if necessary) into a sterile flask. Add 10 ml. of 0.5% *w/v* sterile solution of neutral red. Tube in quantities of 10 or 15 ml., plug and sterilise by steaming at 100° for 30 minutes on 3 successive days.

11. Nutrient Agar Medium. Rub 10 g. of peptone, 5 g. of sodium chloride, and 20 g. of powdered agar into a paste with 150 ml. of distilled water. Add 5 g. of Lab-Lemco dissolved in 500 ml. of distilled water and place in a flask on a water bath. Bubble steam through until the agar is dissolved and adjust the volume to 1 litre with boiling distilled water. Determine the amount of sodium hydroxide required to adjust the medium to pH 7.4 and slowly add the necessary quantity of N/1 sodium hydroxide. Allow to cool to 60°. Thoroughly whip the whites of two eggs and add to the medium. Steam at 100° for about one hour to coagulate the egg albumen, and filter (using a hot-water funnel if necessary) into a sterile flask. Tube in quantities of 10 or 15 ml. and sterilise by steaming at 100° for 30 minutes on 3 consecutive days.

12. Nutrient Broth. 10 g. of peptone rubbed into a cream with water is added slowly to a boiling solution of 5 g. of meat extract (Lab-Lemco) and 5 g. of sodium chloride in 750 ml. of water. The liquid is autoclaved for 30 minutes at 115° and filtered, cooled and adjusted to 1 litre. An aliquot portion is titrated at 37° with N/10 sodium hydroxide until neutral to phenolphthalein and the calculated quantity of N/1 sodium hydroxide is then added very slowly to the remainder to render it neutral to phenolphthalein at 37°. The mixture is heated to boiling and filtered while hot. By the addition of N/1 hydrochloric acid the reaction is adjusted to pH 7.6 using phenol red as indicator. It is then placed in a plugged flask and autoclaved again.

The final reaction of the broth should be between pH 7.2 and pH 7.8.

13. Nutrient Broth for anaerobic test for sterility. Minced lean beef is boiled with water (containing a little sodium hydroxide to neutralise the meat acids) and the aqueous liquid decanted off. The residual fibre is repeatedly boiled with water until all fat and alkali are removed. The residue is drained free from liquid and placed to a height of 1 cm. in test tubes and nutrient broth for aerobic test is added, and the tubes are plugged and sterilised by autoclaving. After sterilisation the reaction of the medium must lie between pH 7.2 and pH 7.8.

Before using for anaerobic testing, the medium should be heated to 100° to free it from dissolved oxygen and then cooled.

14. Nutrient Broth for Rideal-Walker Test, see Standard Rideal-Walker Broth, p. 646.

15. Nutrient Gelatin Medium. Rub 10 g. of peptone and 5 g. of sodium chloride into a paste with 150 ml. of distilled water. Add 5 g. of Lab-Lemco dissolved in 500 ml. of distilled water and to the mixture add 100 g. of sheet gelatin cut into small pieces. Heat on a water-bath and pass steam through the mixture until the gelatin has dissolved. Adjust the volume to 1 litre with hot distilled water. Ascertain the pH of the medium by titration of an aliquot portion with standard sodium hydroxide solution. Allow to cool to 60°. Thoroughly whip the whites of two eggs and add to the medium. Steam at 100° for about one hour to coagulate the egg albumen and filter into a sterile flask. Tube in quantities of 10 ml. and plug. Sterilise by steaming at 100° for 30 minutes on each of 3 successive days.

16. Peptone Water (Dunham). Rub 10 g. of peptone and 5 g. of sodium chloride into a smooth paste with 250 ml. of distilled water heated to 60° and adjust to 1 litre with cold distilled water. Steam at 100° for 30 minutes, filter through paper, tube in quantities of 10 ml. and plug. Sterilise by steaming at 100° for 20 minutes on 3 consecutive days. The pH need not be adjusted unless the medium is intended for the isolation of cholera vibrios when it should be adjusted to pH 8.4.

17. **Potato Medium.** Fairly large potatoes should be selected, well washed and scrubbed with a stiff brush. Peel, and remove the "eyes". Using a large-sized cork borer (preferably silver-plated, because steel will cause discolouration) cut cylinders. Then slice each cylinder from end to end, forming wedge-shaped pieces. Place each piece in a sterile test tube with a small plug of wet sterile cotton wool at the bottom. Plug and sterilise by steaming at 100° for 20 minutes on each of five successive days.

18. **Protein-free Broth (Uschinsky).** Sodium chloride 5.0 g., calcium chloride 0.1 g., magnesium sulphate 0.2 g., potassium acid phosphate 2.0 g., potassium aspartate 3.0 g., ammonium lactate 6.0 g., distilled water to 1000 ml. Dissolve and add 30 ml. of glycerin. Tube, and sterilise by heating at 100° for 20 minutes on each of three successive days.

19. **Trypsin Broth (Douglas and Hartley).** Add 500 g. of finely minced lean beef (or ox-heart muscle freed from fat) to 1 litre of water. Heat to 100° for 30 minutes to destroy antitryptic properties of muscle. Add 20 ml. of 1% sodium hydroxide solution. Cool to 37°, add 10 ml. of 1% trypsin and maintain at 37° for 6 hours with frequent shaking. Apply the biuret test and when positive allow to stand overnight, siphon off the clear liquid, filter, adjust to pH 7.2 (Douglas) or pH 8.0 (Hartley) and sterilise by steaming at 100° for 20 minutes on 3 successive days.

For other media described in the text consult the Index.

STERILISATION

Sterilisation, or the preparation of sterile material, is the removal or killing of living organisms. Removal may be accomplished by filtration through a bacterial filter, and killing may be done by dry heat, moist heat, disinfectants or a combination of the methods. The following are important factors affecting the viability of bacteria:—Temperature, the presence or absence of water, the presence or absence of food material such as proteins and carbohydrates, the hydrogen ion concentration of the medium and the presence of disinfectants.

Temperature. The optimum temperature for the growth of pathogenic organisms is 37°. **Non-sporing** organisms are all killed by heating at 60° for 1 hour in the presence of water (i.e. moist heat). This is a maximum temperature for all such organisms. Some succumb at much lower temperatures, e.g. gonococci, which are killed at 47° in a few minutes. A possible exception is *Streptococcus faecalis* which is said to require a slightly higher temperature than 60°. The usual infection in preparing sterile material and solutions is from the hands and is generally a staphylococcus (such as *S. albus*) which may be killed by heating at 80° for 10 minutes. ***This short heating process is recommended as a safety precaution after packing and sealing the product in its final container provided the active substance is stable at that temperature.***

Sporing organisms require a higher temperature than non-sporing. No spores will survive a temperature of 115° of moist heat for 30 minutes (using an autoclave) or a temperature of 121° of dry heat for 1 hour.

Bacterial growth usually ceases below 10° but it appears to be impossible to kill at low temperatures. Bacteria exposed to

evaporation of liquid oxygen (-190°C) and liquid hydrogen (-252°C) were not killed.

The following temperatures are of interest.

0° to 10°	Most bacteria will survive without multiplying for long periods. Organisms will remain alive longer at this temperature than at room temperature.
12° to 15°	Average room temperature.
22°	Optimum temperature for growing moulds and saprophytes.
37°	Blood heat. Optimum temperature for growing pathogenic organisms.
42° to 45°	Optimum temperature for enzymic reactions.
56°	Highest temperature to which blood serum and enzymes can be heated without destruction. Most of the above begin to deteriorate after 10 minutes at this temperature.
60°	Lowest temperature which will ensure the killing of a bacterial emulsion for vaccines (will not kill spore-bearing bacteria).
65°	Proteins begin to coagulate, and all are coagulated at 80° .
100°	Moist heat. 5 minutes kills vegetative bacteria.
115°	Moist heat for 30 minutes will guarantee sterility.
150°	Minimum temperature for 1 hour to ensure sterilisation with dry heat.
160°	Highest dry temperature which will not char cotton fabric.

Hydrogen Ion Concentration. Bacteria have an optimum pH for growth, usually about pH 7.0, whilst on either side of this optimum point there are limits beyond which they fail to survive. These vary with different bacteria. Thus:—

	Acid Limit pH	Optimum	Alkaline Limit pH
<i>B. coli communis</i>	4.4	6.0 to 7.0	7.8
<i>B. cholerae</i>	5.6	6.2 to 8.0	9.6
<i>B. paratyphosus</i>	4.0	6.2 to 7.2	9.6
<i>B. perfringens</i>	4.7	—	11.1
<i>B. prodigiosus</i>	5.0	6.0 to 7.0	8.0
<i>Streptococcus viridans</i>	7.3	7.6 to 7.8	8.3
<i>B. typhosus</i>	4.0	6.2 to 7.2	8.7
<i>Staphylococcus aureus</i>	5.6	7.2 to 7.6	8.1

The correct pH is therefore an important factor in the medium used for promoting growth. Thus in the preparation of culture media, as in the anaerobic and aerobic broth used in testing for sterility and the standard Rideal-Walker broth used for testing the bactericidal values of disinfectants, it is important to make careful adjustment to pH 7.6 to secure optimum conditions for growth. Conversely an unsuitable pH has an important bearing on the ease of sterilisation. Many pharmaceutical solutions have a pH at or near the concentration unfavourable to infecting organisms. Davis (*Quart. J. Pharm.*, 1934, 381) has shown that the following, even after gross infection with *B. mycoides*, *E. subtilis*, dust from straw packing, *Cl. sporogenes* and a soil filtrate **are sterilised by steaming for 60 minutes**. (The pH of the solutions undoubtedly contributes to the ease of sterilisation.) Atrophine sulphate, codeine phosphate, caffeine and sodium benzoate, normal saline, dextrose 5% and 30%, homatropine hydrobromide, procaine hydrochloride, pilocarpine nitrate, sodium thiosulphate 12%, strychnine hydrochloride, peptone 5%, sodium salicylate 30%, hexamine 20%, amylocaine hydrochloride 5%, soluble barbitone 10%, calcium chloride 5%, morphine hydrochloride, morphine tartrate, phenazone 40%.

The majority of these solutions proved to be sterile after 30 minutes' steaming, but this period was unreliable and should be extended to 1 hour.

The bacterial flora of the human gut may be entirely changed by an alteration of pH . Thus a culture of *Bacillus bulgaricus* or *acidophilus* given as curdled milk is employed as an intestinal antiseptic. Its action is due to the lactic acid-producing bacilli reaching and inhabiting the intestinal tract and producing a pH unsuitable for the development of many putrefactive organisms.

The disinfectant action of soaps depends mainly on the alkali content. H ions are more toxic than OH ions at the same concentration. Krönig and Paul have shown that the disinfectant action of acids in general is proportional to the pH of the solutions. Certain acids have a bactericidal value depending also upon either the anion or the undissociated molecule. Thus Winslow and Lochridge have shown that to produce a 99% reduction in the number of *B. coli* in 40 minutes, benzoic acid was over 10 times as effective as acetic acid and over 70 times as effective as hydrochloric acid.

Sterilisation of Aqueous Solutions and Suspensions. The Pharmacopœia directs that when solutions for injection are dispensed in bulk in several doses in one container, an antiseptic such as 0.5% *w/v* of phenol, or one having the same bactericidal value, should be added. This is to inhibit the growth of any bacteria which may reinfect the solution.

The following are used or recommended as substitutes for 0.5% phenol:—Cresol 0.3%, *p*-chlor-*m*-cresol 0.05%, sodium ethyl mercurithiosalicylate (Merthiolate) 1 in 100,000. The latter, however, is only effective in an alkaline medium and therefore unsuitable for many pharmaceutical injections, although it could be used for sera and vaccines.

Antiseptics should not be added to solutions for *intraspinal* or *intravenous injection* and, because of this, *it is unwise to dispense these in bulk*.

The presence of antiseptics is of great importance in preparations such as sera and vaccines, since very serious fatalities have occurred when this precaution has been neglected. The conditions for growth in such media are ideal, and infecting organisms readily multiply. The same conditions do not occur in many aqueous injections of a pharmaceutical type since *the medicament itself may have a bacteriostatic or even bactericidal action*. Aqueous solutions containing acid quinine salts, quinine and urethane, and caffeine and sodium benzoate undoubtedly possess bactericidal powers, particularly towards non-sporing organisms. Davis (*Quart. J. Pharm.*, 1935, No. 3) quotes experiments on a number of aqueous solutions of common medicaments which after heavy infection with *Staphylococcus aureus* self-sterilised themselves in the cold after 24 hours.

They include the following: Amylocaine hydrochloride 5%, apomorphine hydrochloride 1%, emetine hydrochloride 1%, physostigmine salicylate 1%, sodium salicylate 30%, benzamine lactate 2%, sodium iodide 20%, caffeine and sodium benzoate 25%, quinine and urethane injection, quinine dihydrochloride 5%, neoarsphenamine 2.5%, sulpharsphenamine 2%, solution of adrenaline.

The following *failed to kill* after 1 week: Atropine sulphate 0.12%, diamorphine hydrochloride 1%, morphine tartrate 2%, homatropine hydrobromide 1%, hyoscine hydrobromide 1%, ephedrine hydrochloride 1%, peptone 5%, dextrose 5%, antimony and potassium tartrate 2.5%, calcium chloride 5%, sodium citrate 20%, normal saline, and the water control containing the organism.

The bactericidal action of common medicaments is also reported by Todd (*Pharm. J.*, i/1932, 185) and Perrins (*Pharm. J.*, i/1930, 214).

Autoclaving. The official process (*B.P.* '32) consists of heating the solution in the final sealed container in steam at 115° to 116° (or at 10 lbs. in excess of atmospheric pressure) for 30 minutes. This means exposure to *saturated steam* at this temperature. Saturated steam is more effective than dry steam at the same temperature.

A single exposure to the *B.P.* conditions in an autoclave is sufficient to destroy all bacteria and spores *provided that the temperature is maintained for that period*.

Volumes of solution over 100 ml. are required to have a longer period than 30 minutes. Jackson (*Pharm. J.*, 1934, 181) gives the following periods as necessary to bring the respective volumes to 115°, distilled water in flat-bottomed flasks being used.

Vol. of liquid in ml.	50	100	250	500	1000
Time in minutes	11	15	18	23	28

In the preparation of *injection of sodium chloride and acacia*, the *B.P.* requires a preliminary autoclaving at 121° to 122° for one hour owing to the poor heat conductivity of the solution, and the usually gross infection of the gum. The second autoclaving process is probably unnecessary if reasonable aseptic precautions are taken, steaming being sufficient. It is an advantage to avoid re-autoclaving as the gum tends to give a precipitate

again. Autoclaving is of special value only when applied to aqueous solutions, for the like treatment of oily solutions is only equivalent to heating them in a hot air oven at the same temperature.

Autoclaves are usually fitted with pressure gauges only registering lbs. pressure in excess of atmospheric. It is to be regretted that all are not fitted with a thermometer also as the gauges are liable to become inaccurate with use. The only true check is when gauge and thermometer register the correct corresponding pressure and temperature. The following shows the temperatures corresponding to the various pressures thus giving saturated steam.

<i>Pressure</i> (in excess of atmospheric pressure)	<i>Temperature</i>
5 lb.	109°
10 lb.	115.5°
15 lb.	121°
20 lb.	126°
25 lb.	130.5°

These pressures and temperatures *will not coincide* when

- (a) air remains mixed with the pressure steam;
- (b) insufficient water is placed in the autoclave with the result that the steam becomes superheated and *unsaturated*, and if under this condition, aqueous solutions in unsealed containers are enclosed, concentration will occur.

Precautions in the Use of an Autoclave

- (1) See that sufficient water is placed in the autoclave.
- (2) Do not wire rubber caps on to vaccine bottles containing the solution. The caps will burst during autoclaving. It is advisable to insert a thin copper or silver wire between the cap and bottle to provide an air vent. The cap may be wired on after cooling in the autoclave.
- (3) Allow steam to issue freely from the steam cock for several minutes before shutting down in order to drive the air out of the autoclave. An aqueous solution in an unsealed container should be placed in the autoclave when the water in the latter is boiling otherwise there may be an appreciable concentration occurring during the process of driving out the air. This precaution is unnecessary when sealed containers, such as ampoules, are treated.
- (4) Time the immersion from the point when the gauge reaches the correct pressure.
- (5) At the end of the period allow the pressure to come gradually to zero before opening up. If a sudden reduction in pressure made by opening the steam cock, solutions in unsealed containers will boil away vigorously. The autoclave should not remain closed after zero pressure is reached, as further cooling produces a negative pressure which may strain the gauge.

(6) Rubber capped vaccine bottles should be allowed to cool in the autoclave. If capped whilst hot, the caps tend to sink on cooling.

An autoclave suitable for small scale work is the Sankey. For an account of this see Greenish and Holder (*Pharm, J.*, i/1932, 355).

Surgical Dressings. If the dressings are loosely packed, sterilisation can readily be carried out by autoclaving at 115° for 30 minutes, subsequently drying in hot air. The problem is more difficult with highly compressed dressings, as neither steam nor heat readily penetrate them. Sterilisation can only be effective if the steam reaches the centre of the package at 115° for 30 minutes. In order to prove penetration small tubes (**witness tubes** or **tubes témoins**) may be inserted into an average sample. The tubes contain a material which changes colour at a definite temperature.

The following are suitable:—

Terpin hydrate with 0.1% methylene blue, melts at 115° and changes to an even blue colour.

Acetanilide (113°) and methylene blue.

Sulphur (115°).

These witness tubes do not indicate the duration of the heating.

In order to produce effective penetration the autoclave must be fitted with an air extractor for producing a vacuum so that air may be extracted prior to the admission of the steam pressure (at 10 lb.) and to withdraw the steam from the interior at the close of the operation. Also in order to prevent the dressings being left in a moist condition the sterilising chamber is surrounded by a jacket which also contains steam, but at a higher pressure, thus ensuring **dry** steam in the sterilising chamber. Thus dry steam is removed from the dressings by the vacuum and afterwards a current of hot air is passed through to sweep the steam from the chamber. This effectively dries the dressings and completes the process. Autoclaving may also be used for glassware, towels, metal instruments and rubber goods.

Rubber Gloves. The effect of various methods of sterilisation on surgical rubber gloves is incorporated in a new standard specification for these articles published by the Standards Association of Australia. After prescribing the quality, finish, dimension and weights, the report gives details of the loss of tensile strength and extensibility of gloves after sterilisation processes of dry heat, boiling and autoclaving. Each process was repeated at definite intervals. The conclusions reached were that the hot air oven method is the most severe, as an almost complete loss of tensile strength was noted after ten sterilisations. Autoclaving at 15 lb. pressure was found to be less severe, but nevertheless to show a serious loss of tensile strength from 2600 lb. per sq. in. to 1700 lb. after five sterilisations and to 1100 lb. after ten sterilisations (1500 lb. was laid down as the minimum tensile strength after sterilisation). The loss after boiling for 15 minutes was found to be negligible.

Steaming. This process consists in immersion in flowing steam (sometimes called streaming steam) in an ordinary pressure fish kettle, or more elaborate apparatus such as the Koch steriliser designed to condense and reflux the steam (see also *Pharm. J.* 1935, 116). Steaming is not an official process. This is to be regretted, as it was the old method of sterilising and is quite efficient in many cases. Davis (*Quart. J. Pharm.*, 1934, 38) has shown it to be effective, sterilisation being complete in 6 minutes even though the solutions were heavily infected with bacteria (see p. 634). These results have been confirmed.

Dry Heat. Sterilisation may be effected by heating to 150° for 1 hour in a hot air oven. This method is suitable for apparatus, oils, fats, waxes and dry chemicals or powders, provided the temperature can be borne without detriment.

Apparatus. Bottles, mortars, measures, pipettes, ampoules etc., should be well cleaned before being sterilised. This is very important with glass apparatus used for the first time as any greasy layer may reduce the efficiency of the sterilisation process. Use soap and hot water, rinsing with distilled water, or use a solution of potassium dichromate 6 in sulphuric acid 4 and water 30, finally rinsing thoroughly with distilled water. The apparatus is then heated in a hot air oven at 150° for 1 hour. Care should be taken that both heating and cooling are not too sudden. **Rubber in any form will not stand this treatment.** Rubber goods should be autoclaved or boiled. The oven may be electrically or gas heated with thermo controls but it can be improvised. A shelf or false bottom perforated, or otherwise arranged for air circulation, must separate the articles from the bottom plate whereon the flame plays. **It is advisable to prepare a supply of sterilised apparatus** and to keep it in a special cupboard, which should be reasonably dust-free. Flasks and bottles for such stock should be either plugged with non-absorbent wool or capped with paper and tied with twine before placing in the oven. Other apparatus should be wrapped in paper (newspaper is quite suitable) or cloth. All wrappings must remain on until the apparatus is required for use. Alternatively the apparatus (including rubber tubing, bungs and surgical rubber gloves) may be sterilised by autoclaving at 115° for ½ hour. The apparatus should be capped or wrapped before autoclaving and afterwards immediately dried (whilst still wrapped) in an oven at about 60° to 70°. **Mortars and pestles** can be sterilised by well washing with soapy water, rinsing with alcohol and drying by flaming with a bunsen burner. Pestles with wooden handles will not stand 150°, since the cement fixing the head may melt.

Oils, Fats and Waxes (including liquid, soft and hard paraffins). These can only be sterilised by heating to 150° for 1 hour in a hot air oven. Wool fat intended for injection should always be so treated as from the nature of its source there is the possibility of contamination with anthrax and tetanus. Ca

should be taken not to overheat vegetable oils such as olive oil, since partial decomposition may occur. It is advisable and convenient to allow oils to filter through filter paper whilst sterilising in the oven. The efficiency of the method is confirmed by Coulthard and by O'Brien and Parish (*Quart. J. Pharm.*, 1935, 90, 94). Coulthard stresses the importance of ensuring that the oil reaches 150° , and the fact that it is unwise to rely on oven-temperature only. The thermometer should dip into a control quantity of oil in the oven so that the temperature indicated would be that of the oil. Samples of olive and almond oils so treated showed no significant deterioration, no increase in the acid value being noticeable.

Oily Intramuscular Injections such as *Injectio Hydrargyri B.P.* The main precaution is to sterilise the wool fat and oil with heat. Creosote or phenol has very little bactericidal value in oil.

Dry Chemicals and Powders. For these dry heat is best, preferably 150° for 1 hour, provided the physical characters (decomposition, m.p., volatilisation, loss of water of crystallisation, etc.) of the substance permit. The chief problem is to obtain effective heat penetration owing to the poor conductivity of such material, hence powders should always be spread out in a thin layer in the oven. Kaolin (like wool fat) should always be suspect as from the nature of its source it may contain tetanus spores. It is best sterilised by being spread out in a thin layer on paper in the oven and heated to 160° to 170° for one hour. It may then be tipped quickly into a sterilised, wide-mouthed, stoppered bottle, care being taken to avoid undue exposure to reinfection whilst doing so. Zinc oxide may be similarly heated. (As a guide to temperature, paper and cotton wool turn yellow at about 165°). Tawell advises sterilising boric acid by prolonged heating at 98° in a carefully regulated oven. It is liable to undergo change if heated much above 100° .

Tyndallisation. This consists in heating the solutions in sealed containers at 80° for 1 hour on 3 successive days, and is applicable to substances which are unstable at higher temperatures, such as salts of cocaine, atropine, etc. The process is based upon the theory that the vegetative forms of bacteria will be readily killed at 80° , but any spores will survive. These, however, will change to the vegetative form during the resting period and will be killed in the subsequent reheatings. The process is usually too long for practical purposes and has, moreover, been seriously criticised as being unreliable. The success of the process depends upon whether or not the spores actually do develop into the vegetative form during the resting period. Such development during this period will only occur if optimum conditions prevail, such as the presence of nutrient material, a suitable pH and the absence of any substances having a bacteriostatic action. If any of these factors is absent then there may not be any change from

the spore condition and the process will fail to sterilise. Davis (*Quart. J. Pharm.*, 1934, 381, and 1935, No. 3) reports results of tests on various aqueous solutions when tyndallisation was applied, and shows that when sporing organisms are present the process is most unreliable. When, however, non-sporing organisms were present the first heating at 80° produced a sterile condition in every case and the subsequent heatings were quite unnecessary. He suggests that if the process is retained, it should be controlled by tests for sterility. There is no doubt that the process is effective when the medium is of a nutrient type such as broth. O'Brien and Parish (*Quart. J. Pharm.*, 1935, 94) record the results of tests on the attempted sterilisation of oils by tyndallisation using olive and almond oils and liquid paraffin infected with a spore-containing mixture of earth, hay and fæces, and condemn the method as unreliable. This again is undoubtedly due to the oily medium being unsuitable for development. Tyndallisation can only be effective as a method for preparing the usual type of sterile pharmaceutical solution if good aseptic precautions are taken to avoid spore contamination, including the use of freshly distilled water and previously sterilised containers.

The Emergency Method of Sterilisation. The *B.P.* permits solutions for injection to be prepared in an emergency, directing that the solution shall be prepared by aseptic methods (these are not defined), adding 0.5% of phenol or its bactericidal equivalent, sealing in a container heated, by immersion in water or other means, at 80° for not less than 30 minutes. The solution must be labelled with *the date* and the warning "**Keep in a cool place, and use within four days.**" It is obvious that complete sterilisation is not expected by this method. It is difficult to understand why the Pharmacopœia does not permit solutions of thermostable substance to be raised to 100°. Complete sterility would be assured, especially in the presence of 0.5% of phenol. For an account of the emergency method see Coulthard, *Pharm. J.* i/1933, 316. For solutions for intravenous injections, no antiseptic is permitted the solution being boiled for 15 minutes. Solutions for intrathecal injection must not be prepared by these emergency methods, since complete sterility is most important.

The *B.P.* directs that it is the duty of the dispenser to inform the prescriber if none of the official methods of sterilisation can be applied, and to obtain the prescriber's approval for any method to be adopted.

Ophthalmic Solutions. In dispensing simple ophthalmic solutions required for immediate use, e.g., solutions of atropine and cocaine salts in dropping bottles, it is only practicable to use recently boiled and cooled distilled water which can be used for washing the measure, rod, etc., prior to making the solution. *The containers can be kept ready sterilised in the dispensary.*

Filtration. For sterilisation by filtration the *B.P.* requires control by tests for sterility. This is a wise precaution, since filtration is a skilled operation and demands good aseptic technique. It is probably the best sterilisation process for large scale work and where efficient control is available. For isolated small scale work it is probably too complicated for general use.

The process is the only one for substances such as insulin which are easily inactivated on heating. It can, however, be applied generally except where adsorption of the medicament may occur, as in the case of indigo carmine and methylene blue. The adsorption of substances of this type is apparent by loss of colour, but the possible adsorption of other medicaments by the various types of filters requires investigation. Suitable bacterial filters for pharmaceutical use are the Berkefeld, consisting of a column of diatomite, the Chamberland and the Doulton, which rely on a porous porcelain "candle," and the Seitz, which has a porous asbestos pad. Of these the **Seitz** is most generally used and can be worked with both positive pressure (Manteufel model, using a bicycle pump) or negative pressure (Uhlenhuth model, using a water pump). **Positive pressure is preferable**, since any leakage is outwards with less risk of airborne contamination. New pads are used for each filtration. They cannot be cleaned but their price is such that their use is very economical. The Seitz pad, is, however, open to two serious objections for pharmaceutical use. First, it yields alkalis to water and is not readily washed free. This can easily result in solutions of alkaloidal salts, such as strychnine hydrochloride, diamorphine hydrochloride and morphine hydrochloride, depositing free alkaloid after passing through the filter. This is apparent with such salts but inactivation may occur with such substances as adrenaline, insulin, apomorphine and pituitary, so that precautions must be taken prior to the actual filtration. From tests made it was found that, using a 3 cm. pad (weighing 2.85 g.), if 10 ml. of N/25 H_2SO_4 diluted to 100 ml. with water is drawn through the pad and subsequently followed by 200 ml. of distilled water the final washings have a pH of 6.5, which is quite suitable for the type of medicaments mentioned. The amount of acid required for other size pads may be calculated from their weight.

The second serious disadvantage is the traces of fibre which the pads yield on washing, and the considerable difficulty in obtaining a filtrate free from such contamination. This is a serious objection for intravenous injections. It may be overcome by attaching a small sterile sintered glass filter to the metal outlet of the Seitz filter. This effectively removes the fibres. For details of filtering apparatus using a Seitz filter see White, *Pharm. J.*, 1934, 355.

Porous Porcelain Candles (such as the Chamberland or Doulton). These are made with various porosities. Thus Chamberland L 1 allows all bacteria to pass, being merely a clarifying filter. L 3 stops *C. diphtheriae* and the spores of *B. tetani*, whilst L 5, L 7, L 9 and L 11 arrest all bacteria. Small thimble-shaped white Doulton candles are available for pharmaceutical use, and, whilst as efficient as the Chamberland, filter more rapidly. Porcelain candles may be adapted to positive or negative pressure and can be sterilised by autoclaving, but periodically it is advisable to heat them to about white heat in a muffle furnace (the makers usually specify the temperature most suitable), **allowing them to cool in the muffle**. The latter precaution is very important, as too sudden cooling may result in the development of minute cracks and loss of efficiency. This occasional treatment is necessary to destroy accumulation of organic matter—chiefly dead bacteria—and also to guard against

infection of the interior of the porcelain by embedded bacteria as, with prolonged use, some forms of bacteria appear to be able to grow through the material.

For details of apparatus using the Doulton filter, see Sykes, *Pharm. J.*, i/1934, 521.

The Berkefeld filter is adapted to large scale continuous filtration rather than small scale. It is more rapid in action than the Chamberland or Doulton but after continuous use organisms may appear in the filtrate. Horrocks (*Pharm. J.*, i/1901, 1471) has shown that typhoid bacilli will appear in the filtrate in one or two weeks when such contaminated water is being filtered.

Probably one of the best filters for continuous filtration is the **Meta filter** which consists of a column of metal discs with a very fine clearance between them. The apertures are filled before commencing filtration by embedding in the special variety of diatomite from an aqueous suspension. The bed thus formed is the actual filter.

For accounts of sterilisation by filtration, see Hunwicke, *Pharm. J.*, i/1933, 350, and Coulthard, *Pharm. J.*, i/1933, 286, 338.

Aseptic Precautions. It is an advantage to reduce the risk of infection of solutions for injection to a minimum during the process of preparation and sterilisation. It is especially important to take these precautions when conducting sterilisation by filtration, or when broth media or preparations containing them are being handled.

Hands should have nails carefully attended, and kept short and clean, being well scrubbed with soap and water. Scrubbing with soap and water has no bactericidal value and will not sterilise the hands. It may in actual fact increase the number of bacteria by bringing them to the surface from the lower layers of skin. *Tests show this to be true.* It will, however, remove dirt which may be well contaminated with sporing organisms. The following have been recommended for hand disinfection:—tincture of iodine (painting the finger tips), a solution of mercuric iodine 1 : 1000 in alcohol, alcohol 70%. None of these can be relied upon for keeping the skin sterile and moreover the continued use of such reagents may lead ultimately to a dermatitis so that, as a precaution, attempts to sterilise the skin are not worth while. Hand infection from scrubbed hands usually consists of staphylococci which are readily killed by heating the finished product at 80° for 10 minutes.

Clothing. White overalls washed at frequent intervals should be used and should be kept in a cupboard in the laboratory. This precaution lessens the danger of contamination from clothing exposed to street dust.

Air. It is important to realise that bacteria are chiefly dust borne, and any precaution which results in the removal of dust from the atmosphere will render the latter reasonably free from organisms. Dust may be removed by (a) filtration or (b) steam sterilisation. The room should be designed so as to avoid unnecessary ledges on which dust can collect, and the walls, benches, floors, etc., should be such as to permit of frequent washing with an antiseptic.

When filtration is relied upon, the air is usually drawn in through a cotton wool filter or through an oil filter, and a positive pressure is maintained in the room so that when a window or door is opened air escapes outwards and dust cannot enter.

The deposition of dust by steaming can be carried out by creating a slight cloud of steam from the ceiling in the room by attaching rubber tubing to a kettle or boiler. As the moisture settles it will carry the dust down. The following are results of steaming carried out in the serum preparation laboratory of a London hospital, counts being made on agar plates exposed for a definite time.

	Count
Before steaming	15
During steaming	45
$\frac{1}{2}$ hour after steaming	2
2 hours after steaming with 2 persons working	3

Restriction of number of workers. The laboratory should be restricted to those who are actual operators, as every additional person means extra contamination.

For small scale work when a special room is not available, and the work has to be done in the ordinary dispensary, an excellent method is to use a case with sliding doors, similar to a fume cupboard (without the fume vent), the interior of which can be washed and is not subject to the same dust deposition as the remainder of the room. Such precautions are advisable if filtration sterilisation is employed. For similar apparatus see Gunn, *Pharm. J.*, i/1935, 327.

It is a good routine precaution to use distilled water freshly collected from the still for the preparation of injections of an ordinary type. The still should be frequently overhauled and cleaned. For the preparation of intravenous and intrathecal injections the special redistilled sterilised water should be used.

Medicaments. A simple precaution which can and should be taken is to keep all medicaments likely to be used for the preparation of injections in bottles filled with a type of stopper which prevents dust falling between the stopper and the neck, and also to reserve such stock for this special purpose by keeping it in a separate cupboard reasonably dust-free. Such stock should not be used for ordinary dispensing purposes such as the preparation of mixtures, pills and powders. Most medicaments when stored in ordinary stoppered dispensing rounds can quickly become infected in the daily routine of dusting, since dust will be driven between the neck and stopper.

DISINFECTANTS

The bactericidal or bacteriostatic efficiency of disinfectants is a subject which is assuming greater importance every year, for apart from their use in hygiene and surgery, their use in the field of curative medicine is steadily increasing. Our present knowledge of these substances is very incomplete; the value of many published experiments cannot be assessed because of the omission of important details of procedure, yet an exact knowledge is very

essential because of the important rôle they are called upon to play and the great dependence placed upon them.

In devising tests for bactericidal action the following factors must be taken into account:

(a) **The concentration of the disinfectant.** It does not follow that by doubling the concentration, the time of disinfection is halved.

(b) **The time during which the disinfectant is in contact with the test organism.** This will vary with other factors such as temperature and concentration, but it must be recognised that some substances can exert a high bactericidal power if sufficient time be given. Thus mercuric chloride is capable of acting as a bactericide even in high dilution (1 in 400,000) if sufficient time is allowed for the action. Similarly acriflavine requires a long period to demonstrate its value.

(c) **The temperature at which the test is conducted.** The velocity of bactericidal action will increase with rise of temperature but again will vary with the substance. Thus the velocity of action of mercuric chloride is increased threefold by a rise of temperature of 10° , whereas that of phenol is increased sevenfold.

(d) **The organism chosen as the test organism.** Most disinfectants vary in their bactericidal power towards different organisms. Thus phenol is much more active against streptococci than against staphylococci. It is essential, therefore, to select one particular organism if comparisons are to be made. One organism, however, may exist as different strains of appreciably different resistance towards one particular disinfectant. Hence it is further necessary to specify the strain of the test organism, and in order to get complete concordance the organism should always be subcultured under standard conditions through several generations. Two organisms are in common use for such test purposes, *B. coli* and *B. typhosus*. The latter has been chosen for the Standard Rideal-Walker test because of the greater reliability of its strains, the ease with which it grows on agar and also because it is an organism which it is desired to destroy in practice. It forms a fairly uniform suspension in broth culture. *B. coli* on the other hand is non-pathogenic, and the use of MacConkey's bismut salt medium for culturing the test mixtures practically eliminates accidental contamination. *B. coli* is the organism used in the *Lancet* modification of the Rideal-Walker test.

(e) **The presence of other substances having a modifying action.** The bactericidal value of a disinfectant may be considerably modified by the presence of other substances. Thus sodium chloride present in the phenol solution will increase the value, whilst alcohol and glycerin will lower it. Koch has shown that phenol when dissolved in vegetable oils has practically no value. McMaster (*J. inf. Dis.*, 24, 378) has shown that mineral oils such as liquid paraffin do not show this effect. The efficiency of phenol in liquid paraffin is nearly as great as in aqueous solution. T

effect of the presence of protein matter such as serum, blood and faecal matter is of great importance in assessing the value of a disinfectant. Substances which react with protein matter usually have a much lower bactericidal value in its presence than in aqueous solution. Thus the value of mercuric chloride is reduced by 90% in the presence of serum. Formaldehyde and solutions of hypochlorites, e.g., Dakin's solutions or compounds of a similar type, such as chloramine, react very quickly with protein and their bactericidal value drops correspondingly. Iodine will kill streptococci in a few minutes at a dilution of 1 in 120,000 in distilled water, but the addition of 5% of blood requires a concentration of 1 in 1000, and 50% of blood 1 in 200, to prevent actual growth (Fleming, *Proc. roy. Soc.*, Ser. B, 1924, 171). The value of crystal violet and brilliant green against staphylococci suffers a big reduction in the presence of serum. Phenols and cresols, however, are very little affected by the presence of protein and the bactericidal value of acriflavine and related compounds actually *increases* in the presence of serum. Urea, uric acid, fats, alkalis and acids will also affect the action of disinfectants. These reactions in protein media are of great importance in selecting a disinfectant for a particular use. The uses can be very variable, for disinfectants may be required for (1) the sterilisation of apparatus and surgical instruments; (2) the disinfection of excreta, drains, utensils, closet pans, soiled linen and the washing of walls and furniture; (3) the preservation of vaccines and sera against possible bacterial contamination in the presence of a considerable amount of soluble protein matter; (4) the disinfection of wounds.

It follows from these considerations that no one disinfectant can be satisfactory for every purpose and it is essential to use them in an intelligent manner by studying the type of work required from them. It also follows that there can be no one standard test which will give the bactericidal value for a particular disinfectant for all the conditions in which it may be applied.

Standard Methods of Testing Disinfectants

There are two standard tests in use (a) the Rideal-Walker which tests the disinfectant in aqueous solution only, and (b) the Chick Martin which tests in the presence of faecal matter.

The Standard Rideal-Walker Test. Was first published in 1903 but several modifications of it have been introduced, not only by the authors but by other workers. Since disinfectants are sold on this test it is very essential that the same standard procedure should be followed. The method laid down by the British Standards Institution and prepared under the supervision of the Chemical Divisional Council (B.S.S. No. 541—1934*) is now the accepted standard. Its chief application is for

* Obtainable from The British Standards Institution, 28 Victoria Street, S.W.1. Post free, 2s. 2d.

coal-tar disinfectants. It should be clearly understood that the test merely indicates the value of the disinfectant compared with phenol under the conditions of the tests and expresses no opinion of its value under practical conditions of use. Extended experience has shown that this standardised technique, if carefully followed, will give concordant results in the hands of competent workers. The strictest adherence to every detail is essential, and the test should be performed under reasonably dust-free conditions in the laboratory. All the factors which can cause a variation in aqueous solution are standardised.

Apparatus

The specification includes descriptions of the inoculating loop, temperature of the incubator, pipettes, medication tubes, broth tubes and measuring cylinders and attention is drawn to the fact that all apparatus must be scrupulously clean and sterile immediately before use.

Reagents

The reagents used are (1) Standard Rideal-Walker broth. (2) A suitable culture of *Bacillus Typhosus* obtained from The Curator, National Collection of Type Cultures, Lister Institute, Chelsea Gardens, S.W.1. (3) Standard phenol (carbolic acid) having a crystallising point of not less than 40.5°C.

Standard Rideal-Walker Broth

20 grammes of peptone (Allen & Hanburys' "Eupepton") rubbed to cream with water is added slowly to a boiling solution of 20 grammes of Lab Lemco in 750 millilitres of water; 10 grammes of sodium chloride is added and the liquid boiled for thirty minutes, cooled, and water added to one litre. An aliquot portion is titrated at 37° with N/10 sodium hydroxide until neutral to phenolphthalein, and the calculated quantity of N/1 sodium hydroxide is then added very slowly to the remainder to render it neutral to phenolphthalein at 37°. The mixture is heated to the boiling-point and filtered while hot. By the addition of N/1 hydrochloric acid the reaction of the solution is adjusted to pH 7.6, using phenol red as indicator. The broth is sterilised by heating in an autoclave, filtered when cold, distributed into tubes each containing 5 millilitres, and again autoclaved. The final reaction of the broth is between pH 7.3 and pH 7.5.

Method

The technique of the method is described fully in the specification and an example given of the method of calculating the coefficient. By this method the R.W. coefficient is obtained by dividing that dilution of the disinfectant which shows life in 2½ and 5 minutes but no life thereafter, by that dilution of carbolic acid (1 : 95, 1 : 100, 1 : 105, 1 : 110, or 1 : 115) which shows life in 2½ and 5 minutes but no life thereafter.

The "Lancet" modification of the Rideal-Walker Test. The method is occasionally used as an alternative to that of the Rideal-Walker. It follows the latter in principle except that *B. coli communis* is substituted for *B. typhosus*, the test organism and MacConkey's medium is used for subculturing. The number of time periods is increased, and the maximum length of time during which the disinfectant is allowed to act is also increased from 15 to 30 minutes. The coefficient is obtained by taking the mean of two figures: (a) the weakest dilution of the disinfectant which kills in 2½ minutes, and (b) the coefficient for the 30 minutes' period obtained in the same way.

Details of a large number of experiments with this method on common medicinal substances conducted by W. H. Martindale will be found in the 19th Edition of this volume, p. 266 *et seq.*

The Chick Martin Test (Lister Institute). In this method (*J. Hyg., Camb.*, 1908, 654) the bactericidal value is estimated in the presence of organic matter (dried fæces) against *B. typhosus* for 30 minutes.

The mixed fæces of several healthy individuals on an ordinary diet are dried on a water-bath at 105°, ground to a fine powder in

mortar and passed through a sieve with 130 meshes to the inch. 0.15 g. quantities of the powder are placed in test tubes and to each is added 2.5 ml. of distilled water. The tubes are capped with rubber caps and sterilised by autoclaving at 120° for 10 minutes. If stored, care must be taken to prevent evaporation. At the time of the test different amounts of a suitable dilution of the disinfectant under test are added to each tube and sterile water added to bring the total volume to 5 ml. A series of tubes containing different concentrations of standard phenol in 5 ml. of distilled water *without* faeces is also prepared so that the carbolic acid coefficient can be directly determined.

All the tubes are immersed in a water-bath at 20°. To each tube in the series 5 drops of a 24-hour broth culture of *B. typhosus* are added, an interval of 30 to 60 seconds being allowed between the inoculation of each tube. 30 minutes after the inoculation of the first tube, it is sampled in duplicate by transferring a 3 mm. loopful into each of two tubes containing 10 ml. of glucose broth. The remaining tubes are similarly sampled at intervals of 30 to 60 seconds. The inoculated broth tubes are then incubated at 37°. A reading is taken in 24 hours and is confirmed after 48 hours.

The phenol is tested without faeces and to allow for this a "depreciation factor" of 1.2 is used in working the calculation. The following is a typical test (Hewlett, *Manual of Bact.*, 9th Edn., p. 723).

Diluted Disinfectant, 2% dilution		Phenol 5% solution	
Amount in a tube	Results of 2 subcultures	Amount in a tube	Results of 2 subcultures
0.2	+	0.5	+
0.28	+	0.65	+
0.39	+	0.8	0
0.55	0	1.0	0
0.77	0	1.3	0
1.03	0		
1.51	0		
2.10	0		

The end point is taken as the mean between the last positive and the first negative tubes. The calculation is as follows:—The mean of the disinfectant solution is 0.47 and of the phenol solution 0.72,

$$\text{Phenol coefficient} = \frac{0.72}{0.47} \times \frac{\text{Phenol percentage } 5}{2} \times \frac{\text{Depreciation factor } 1.2}{1} = 4.59$$

(Disinfectant percentage)

The results obtained with phenol are very constant and, using a 2% solution of the disinfectant, the quantities used give a range of 9.0 to 0.8 in the coefficient.

The Chick Martin type of test undoubtedly gives a truer indication of the value of an excremental disinfectant than the Rideal-Walker test. Garrod however (*J. Hyg., Camb.*, 1934, 322), claims that the Chick Martin test as outlined above can give irregular results. He criticises the use of dried fæces as the organic matter, and suggests its replacement with dried, dead yeast because of the more constant average size of these organisms. He claims that the inhibiting factor is the presence of solid particles (and not soluble organic matter) and that subsequent adsorption of disinfectant on these particles. The degree of adsorption will vary with the size. Powdered fæces tend to clump and thus produce size variation. That adsorption does play an important part in the action of disinfection is shown by the fact that the value of a disinfectant can vary with its physical condition according to whether it is used in solution or as an emulsion or emulsoid. *The latter type is the most effective* as the emulsoid particles are adsorbed on the bacteria, thus increasing the concentration in the immediate neighbourhood.

Emulsoids of the cresol group are generally most active when freshly made in solution; after a day or two, probably because of an alteration in their colloidal state, their activity diminishes. It follows, too, that the presence of suspended solids will interfere owing to their adsorptive action.

The Specific Action of Disinfectants. Many disinfectants exhibit variable bactericidal values when tested against different organisms. A knowledge of this specific action is of great importance, since a disinfectant can be chosen for action against the causative organisms in diseases of bacterial origin. This specific action is very apparent in the organic dye series of disinfectants and in many cases it appears to vary according to the staining properties of the organisms. Thus with a mixture of different organisms, it is possible to select a particular disinfectant which will kill off one organism in the mixture and allow the others to grow profusely. Churchman (*J. exp. Med.*, 1912, 221) showed that most of the gram-positive bacteria are very susceptible to gentian violet, crystal violet, malachite green, aniline violet, and safranin, but that the gram-negative bacteria will grow well in concentrations of these dyes which are twenty times as strong. Later he showed that by substituting acid fuchsine or flavine for the gentian violet type the result could almost be reversed and the gram-negative bacteria inhibited while allowing the gram-positive cocci to grow.

The following concentrations are necessary to inhibit the growth of *Staphylococcus aureus* and *B. coli*.

	<i>Staph. aureus</i>		<i>B. coli</i>	
	Conc. in 0·7% peptone water	Conc. in serum	Conc. in 0·7% peptone water	Conc. in serum
Crystal violet	1 : 4,000,000	1 : 400,000	1 : 8000	1 : 8000
Malachite green	1 : 10,000,000	1 : 40,000	1 : 20,000	1 : 1000
Brilliant green (sulphate)	1 : 10,000,000	1 : 30,000	1 : 130,000	1 : 3500
Brilliant green (oxalate)	1 : 10,000,000	1 : 100,000	1 : 200,000	1 : 3500
Flavine	1 : 20,000	1 : 200,000	1 : 1300	1 : 100,000
Phenol	1 : 250	1 : 250	1 : 500	1 : 500
Chloramine-T	1 : 2000	1 : 250	1 : 2000	1 : 250
Mercuric chloride	1 : 1,000,000	1 : 10,000	1 : 1,000,000	1 : 10,000

Very striking examples of specific action were found by Bechhold (*Hoppe-Seyl. Z.*, 47, 194) when using the halogen compounds of naphthol. As members of the series increase in bromine content the specific action changes:—

Compound	Minimal conc. required to kill	
	<i>B. diphtheriæ</i>	<i>B. coli communis</i>
Lysol	1 : 20,000	1 : 800
β -naphthol	1 : 10,000	1 : 8000
Monobrom- β -naphthol	1 : 10,000	1 : 8000
Dibrom- β -naphthol	1 : 40,000	1 : 30,000
Tribrom- β -naphthol	1 : 400,000	1 : 1000
Tetrabrom- β -naphthol	1 : 200,000	1 : 500
Pentabrom- β -naphthol	1 : 150,000	1 : 100

Similar differences were found by Klarmon (*J. Amer. chem. Soc.*, 1932, 3315), with halogen derivatives of monohydroxy diphenylmethane. All were found to be potent bactericides and some showed extraordinarily high efficacy towards *Staph. aureus* and *Streptococcus hæmolyticus*. The same worker has investigated the differences in bactericidal value of alkyl derivatives of *p*-chlorophenol against a number of bacteria and moulds.—*J. Amer. chem. Soc.*, 1933, 2576.

The bactericidal value of several quinine derivatives has been investigated (Morgenroth, *Dtsch. med. Wschr.*, 1918, 44, 961) and some have shown marked specific action upon the pneumococcus.

Minimal dilutions which kill various organisms:—

	<i>B. diphtheriæ</i>	<i>B. tetani</i>	Strep- to- coccus	Sta- phylo- coccus	Pneumo- coccus
Optochin hydrochloride (Ethylhydrocupreine HCl)	1 : 400	1:2500	—	1:500	1:400,000
Eucupin dihydrochloride (Isoamylhydrocupreine HCl)	1:2000	1:20,000	1:40,000	1:8000	1:20,000
Vuzin dihydrochloride (Isoctylhydrocupreine HCl)	1:8000	1:60,000	1:80,000	1:16,000	—

Specific antiseptic treatment of infected wounds has been suggested. Data are given *re* inorganic and organic acids operating on growths of *Streptococcus pyogenes*, *Staphylococcus aureus*, *B. pyocyaneus* and *B. ærogenes capsulatus*. Phenol and cresol are more active against streptococci than against staphylococci and showed very little activity against *B. Welchii*. Quinine hydrochloride showed its greatest activity against the latter and was fairly active against streptococci but had little action on staphylococci—K. Taylor, *Lancet*, i/1917, 294, 306.

A remarkable case of complementary specificity is quoted by Maclean (*Pharm. J.*, ii/1932, 287). The two substances concerned are potassium tellurite and a filtrate from a culture of a mould, *Penicillium*. If the mould filtrate is added to a sample of sputum and the mixture cultured, organisms such as *B. influenzae*, *M. catarrhalis* and coliform bacilli will grow out. If, however, potassium tellurite be used, all the above will be killed but such organisms as streptococci, pneumococci and gram-positive bacilli will grow.

Excremental Disinfectants. Disinfectants to be used for the sterilisation of excreta, sputum, etc., must be substances which retain their bactericidal power in the presence of excess of protein matter. They are usually required to act fairly

quickly, which factor would exclude substances such as acriflavine. Moreover the use is such as demands a reasonably cheap product and for these reasons coal tar products are generally used, either as lysol or as various proprietary preparations consisting of coal tar fractions containing phenolic bodies with some emulgent such as soap or gelatin, so that when added to water a milky emulsion or emulsoid is formed. They include preparations such as Cyllin, Izal, and Jeyes Fluid.

Lysol is now an official synonym in Great Britain and Northern Ireland for *Liquor Cresolis Saponatus B.P.* and as such must contain 50% of cresol. The disinfecting power of the higher phenols increases proportion to their position in the homologous series but their solubility decreases proportionately and the higher ones are, therefore, used in the form of emulsion or emulsoids. (For further details of these substances see Vol. I.) Mercuric chloride is considerably reduced in bactericidal value in the presence of faecal matter, and for the disinfection of typhoid stools very strong solutions are necessary such as 1 in 500 with the addition of 25% of hydrochloric acid.

Sterilisation of the Skin. The problem involved is to kill the staphylococci and penetrate the sweat glands.

It is usually a simple matter to sterilise a patient's skin prior to an operation, since the disinfectant can have a long time to act. There is also no objection to staining the skin. A 2% solution of iodine in 70% alcohol is usually employed and is generally satisfactory since both constituents have a bactericidal value. Difficulties arise when special areas have to be treated such as the vulva and vagina during childbirth. Garrod (*Brit. med. J.*, i/1931, 572) showed that phenol and lysol did not produce the necessary action and concluded that brilliant green was the best bactericide and acriflavine the best bacteriostatic.

Browning and Bonney (*Brit. med. J.*, i/1918, 562) recommended a 1% solution of a mixture of equal parts of crystal violet and brilliant green for disinfection of the perianal region. They found that this mixture when applied 6 hours before the operation sterilised the perianal skin in 15 cases out of 17. It is preferable to iodine since it is non-irritating whilst being actively antiseptic. The *B.P.C.* includes this solution under the name of *Liquor Tinctorium*. The following have also been recommended for skin sterilisation:—

A solution of mercuric iodide and potassium iodide in alcohol 1 in 500 to 1 in 2000 (it is usually coloured pink with eosin)
2% solution of mercurochrome in water 3, alcohol 55, acetone 10
mercuric chloride, 0.08% solution in 70% alcohol.

Disinfection of Wounds. This demands special consideration in the choice of a suitable disinfectant, for whilst destroying the invading organisms it must not at the same time cause injury to the leucocytes and thus prevent phagocytosis, the most important factor in the healing process. The disinfectant with the highest R.W. value is not necessarily the best wound antiseptic. Fleming (*Proc. roy. Soc.*, Ser. B, 1922, 315) has shown the presence of lysozyme in all body secretions, with a bactericidal action so strong that it can compare with 1 in 20 phenol and 1 in 100 mercuric chloride. This natural antiseptic undoubtedly plays an important part in producing a sterile condition of the wound. Maclean (*Pharm. J.*, ii/1932, 287) points out that the bactericidal

value of lysozyme can be destroyed by certain disinfectants such as iodine and hypochlorites, but others such as boric acid and silver proteinates, which have long been used as antiseptics in eye drops, have little inhibitory action on lysozyme. Moreover, a wound disinfectant must be active in the presence of excess of serum or blood, and must not injure the tissues. For these reasons both mercuric chloride and phenol have little value in wound treatment. A very powerful action is not even necessary, for a substance having only an antiseptic action may be of great value in that it can inhibit development of bacteria, leaving the living tissues to destroy them. Browning (*Brit. med. J.*, ii/1917, 70) has investigated the relative action of substances upon bacteria, phagocytosis, and tissue as follows:—

Substance	Conc. which kills <i>S. aureus</i> in serum in 48 hours	Conc. which reduces phagocytosis 50% in 20 mins.	Conc. which produces irritation of the conjunctiva
Proflavine	1 : 150,000	1 : 500	1 : 150
Acriflavine	1 : 150,000	1 : 600	1 : 150
Mercuric chloride	1 : 20,000	1 : 10,000	

This affords an excellent example of the two types, suggesting that the flavine compounds should be good wound antiseptics, because this action can develop at concentrations well removed from those which inhibit phagocytosis or which may produce irritation. It should be remembered, however, that flavine compounds are very slow in their action except in high concentrations and 1 in 20,000 is required to kill *S. aureus* in 2 hours. The *B.P.C.* recommends 1 in 1000 in normal saline. The chief objection to acriflavine is that after prolonged treatment, wounds tend to become sluggish in healing. Acriflavine has also been criticised because of the great affinity which it has for cotton fibre. Cotton dressings soaked in acriflavine solutions tend to absorb the compound to the detriment of its antiseptic action when such medicated dressings are applied to a wound. Mercury and zinc cyanide gauze has not this disadvantage. The sterilisation of a wound is more difficult than the sterilisation of blood because in the latter case the question of penetration does not come in. Any antiseptic which is to be effective must have the power of entering possibly deep tissues. (Again metallic salts such as mercuric chloride cannot do this since they are precipitated by protein.) This can only be done by setting up a lymphagocic action which will cause fresh fluid to flow into the wound and carry the bacteria to the surface and into contact with the antiseptic. Hence the value of normal and hypertonic saline, and glycerin and magnesium sulphate associated with antiseptics.

Glycerin has long been so used, and several references to it occur. *Phillips* (*Lancet*, ii/1924, 1229, 1307) draws attention to its useful lymphagogenic action with the addition of iodine in labour. *Salmond* (*Lancet*, ii/1929, 660) suggests that glycerin should be used for controlling hæmorrhage in Cæsarian section and promoting drainage of the uterus during the puerperium. After removal of the placenta the cavity is swabbed out with glycerin.

Carrel (*Treatment of Infected Wounds: Military Med. Man.*, London, 1918) introduced the treatment of wounds by continuous irrigation with solution of hypochlorites, the first being eusol, which proved, however, to be too irritating and unstable. Later, **Dakin's solution** (now official in the *B.P.*) was substituted and also **Chloramine**. The latter forms a nearly neutral solution, relatively non-irritating and quite stable. A 2% solution is usually employed. In order to obtain satisfactory results the supply of hypochlorite must be renewed continuously, since the available chlorine is rapidly exhausted by interaction with the proteins in the suppuration. Some of the hypochlorites act as lymphagogues but only because of the irritation they set up in the tissues.

Dichloramine, which is oil soluble and can be used in concentrations of up to 10%, can be left in contact with wounds for prolonged periods. Wounds are packed with gauze soaked in the solution. It acts like chloramine by giving up chlorine to the watery discharge, and the dressing only requires renewal once every 24 hours.

Bismuth and Iodoform Paste, B.P.C. (B.I.P.P.) is still used for packing wounds. This has been criticised as being ineffective (*Garrod, Pharm. J.* ii/1935, 323).

Hydrogen Peroxide readily kills bacteria in the absence of excess of protein because of the nascent oxygen it liberates (*Krönig and Paul* have shown that a 3% solution kills anthrax spores in an hour), but when applied to wounds it is inactivated by the protein present. It is, however, a very valuable agent for cleaning suppurating wounds because of the mechanical action of the liberated oxygen which disturbs the deposits of pus.

Iodine, whilst a good disinfectant for the intact skin, may be unreliable for wounds. *Fleming* (*Proc. roy. Soc.*, Ser. B., 1924, 171) has shown that in the presence of 50% of blood a concentration of 1 in 200 is required to inhibit streptococci whilst 1 in 120,000 will kill in aqueous media without blood.

Cresols and Halogen Derivatives of Phenols, Cresols and Xylenols

Compounds of this type are now being introduced which act as effective bactericides at dilutions which are well removed from those which damage tissue. It is very probable that they will prove to be excellent wound antiseptics.

Brilliant Green. A paste containing brilliant green 1, boric acid 275, purified talc 25, and liquid paraffin 200 is used for filling wound cavities. Brilliant green may also be used for irrigating wounds by *Carrel's* method instead of *Dakin's* solution.

Classification of Disinfectants and Antiseptics

The following is a classification of the varied uses of disinfectants; details of the action and special uses of each will be found in Vol. I in the monograph of the particular substance.

General

Excremental and for bedding, utensils, etc.

Mercuric chloride, lysol, phenol, coal tar fractions, zinc chloride.

Gaseous (for fumigation of rooms).

Chlorine, cresol, formaldehyde, paraformaldehyde, phenol sulphur.

For Local Application

Skin sterilisation before operation.

Acridine, alcohol, hexyl-resorcinol, mercuric iodide, mercuric oxycyanide, mercuric chloride, iodine, lysol, mercurochrome, methyl violet, brilliant green, trinitrophenol.

For Open Wounds

Boric acid, acriflavine, euflavine, mercury and zinc cyanide, mercuric iodide, iodine, mercuric chloride, ichthammol, hydrogen peroxide, Dakin's solution, chloramine, dichloramine, potassium permanganate, trinitrophenol, zinc sulphate.

GAS POISONING

The hazard of gas poisoning in peace-time is mainly restricted to carbon monoxide, coal gas, carbon dioxide and certain risks associated with specific industries, but in warfare the scope is widened considerably.

The term "gas" in this connection is not limited to its usual physical sense but includes gases, liquids or solids—in fact any chemical substance which can be dispersed into fine particles. A classification into two main divisions can be made according to whether the agents are persistent—e.g., liquids which evaporate slowly—or non-persistent, such as gases and "smokes" which are more or less quickly dissipated by air movement and by diffusion.

Chemical warfare was initiated by the Germans in 1915 by the liberation of chlorine in the form of a cloud, but subsequently the use of shells, trench mortars, bombs and grenades formed the chief methods of distribution. To these must be added the use of smokes produced by heating certain arsenicals in stationary generators. Future developments must include distribution from the air either in the form of bombs, from some type of spraying mechanism, or through the exhaust of aeroplanes.

The effect produced is proportional to the concentration and time of exposure, the former obviously being dependent upon meteorological conditions such as low wind velocity, moderate temperature, absence of heavy rain, and a fairly high humidity.

Classification According to Principal Effect

Vesicants. Gases, liquids or solids which damage any part of the body with which they come into contact. The chief effects are acute conjunctivitis, nausea, vomiting, erythema of exposed surfaces, followed in severe cases by blistering and inflammation of the trachea and bronchi. The danger is enhanced by marked delay of onset of the symptoms, and the burning due to these agents is characterised by delay in healing. Deaths are due more often to secondary bacterial infection of the damaged areas than to direct poisonous effect.

Mustard Gas, dichlorodiethyl sulphide, $(\text{CH}_2\text{Cl}\cdot\text{CH}_2)_2\text{S}$. This substance was the only one of this group used during the War. It is a heavy, viscid liquid possessing a faint alliaceous odour. M.p. $14\cdot5^\circ$; b.p. 217° ; sp. gr. at 15° , 1.28. These physical properties illustrate its persistent nature, and contaminated ground may remain a danger for considerable periods of time. It is also absorbed by clothing. It is slightly soluble in water, and the solution formed is dangerous to handle. Chemically, the compound is fairly stable; it is hydrolysed by boiling water or by steam and is decomposed by chlorination. These facts point the way to the methods used for decontamination. Mustard gas is a very poisonous

substance but its action is local—it is a direct irritant to skin and mucous membranes. The rapidity of its penetration is probably due to its high solubility in lipoids.

Lewisite, chlorovinyldichloroarsine, $\text{CHCl}=\text{CH}\cdot\text{AsCl}_2$. This substance was isolated by the American Chemical Warfare Service and has not yet been used. It is a liquid with an odour recalling that of geraniums. M.p. 13° ; b.p. 190° . It is soluble in the ordinary organic solvents and is hydrolysed by water and alkalis. Lewisite is a sensory irritant and is also capable of producing burns similar to those of mustard gas; the lesions, however, heal more quickly, though if extensive they may be complicated by the danger of arsenical poisoning.

Treatment. Eyes: bathe with lukewarm solutions of boracic acid, normal saline or 2% sodium carbonate. Drops of liquid paraffin. If severe, in addition to frequent bathing use sterilised 1% atropine ointment. Skin: treatment similar to that for thermal burns complicated by continuous flow of serum, liability to sepsis and marked delay of healing. Cleanse the skin thoroughly, remove the blister aseptically and apply evaporating lotions, benzocaine and a dusting powder and 5% potassium permanganate solution.

Lung Irritants. The term is self-explanatory and all of this type produce pronounced effects on the alveoli of the lungs, with the danger of acute pulmonary œdema.

Phosgene, carbonyl chloride, $\text{O}=\text{CCl}_2$. Phosgene is an intermediate in several chemical processes and hence the risk is not restricted to chemical warfare. One of the most unfortunate aspects of poisoning with this substance is that the appearance of serious symptoms may be delayed for several hours. It is a colourless gas which fumes in moist air owing to hydrolysis. M.p. -123° ; b.p. 8° . Chemically, the compound is not very stable towards hydrolytic agents. Water, alkalis and hexamine catalyse its decomposition.

Chlorine. This substance is encountered in industry; it is more irritant than phosgene, symptoms of poisoning are not subject to delay of onset, and a high concentration is required to produce severe pulmonary œdema. The liquid phase is further removed from normal conditions and hence it is not subject to such slow evaporation as phosgene.

Chloropicrin, $\text{CCl}_3\cdot\text{NO}_2$. This substance is a liquid with a boiling-point 112° (m.p. -69°) and it is therefore semi-persistent; contaminated areas may remain dangerous for more than 12 hours. It is a stronger lachrymator but less toxic than phosgene; it is more toxic and more effective as a sensory irritant than chlorine. Its action is cumulative, and frequent exposure to small concentrations weakens resistance. In addition, it may be regarded as a vesicant since by contact it is capable of producing ulceration and conjunctivitis.

Chemically, it is comparatively stable but is decomposed by sodium sulphide.

Other Lung Irritants

Substance	Formula	B.p. $^\circ\text{C.}$	M.p. $^\circ\text{C.}$	How used	Decom- posed by	Re- marks
Bromine	Br_2	63	-7	Grenades	Alkalis $\text{Na}_2\text{S}_2\text{O}_3$	
Brom- acetone	$\text{CH}_3\text{COCH}_2\text{Br}$	136	-54	Shells	Alkalis $\text{NaBrO} + \text{Na}_2\text{CO}_3$	
Cyanogen bromide	CNBr	61.5	52	Shells	Alkalis	
Chloro- methyl- chloro- formate	$\text{Cl}\cdot\text{COOCCl}_3$			Shells	Alkalis	As toxic as phos- gene
Phenylcarby- lamine chloride	$\text{C}_6\text{H}_5\text{NCCl}_2$	20		Shells	Alkalis Hexamine	Delay action

Treatment. One of the most important first steps is to prevent undue muscular exertion, because the patient suffers from a deficiency of oxygen and a retention of carbon dioxide. For the same reason the patient should be kept warm. Oxygen should be administered continuously during the first few days through some such mechanism as the Haldane apparatus (see *Brit. med. J.*, 1917, 181). In certain acute cases, venesection up to 20 oz. has been found to give relief.

Although oxygen is the best cardiac stimulant some help may be derived from the following: pituitary (posterior lobe) extract 0.5 ml. hypodermically at 3-hourly intervals; camphor 1 grain, olive oil 5 minims, ether 5 minims, 10 to 20 minims hypodermically.

The use of atropine, morphine and phenacetin should be avoided.

Sensory Irritants. The substances in this class may be considered as derivatives of arsine, AsH_3 . The toxicity of the arsenium is considerably reduced, but even very small concentrations have an immediate and acutely irritating action upon the sensory nerves.

The compounds are very stable, possess very high boiling points, and are usually dispersed without decomposition, in the form of a toxic smoke, by heating in stationary generators or through the medium of shells.

	Formula	M.p. °C.	B.p. °C.
Diphenylchloroarsine ...	$(\text{C}_6\text{H}_5)_2\text{AsCl}$	43	333
Diphenylaminechloroarsine ...	$\text{C}_6\text{H}_4 \begin{array}{c} \text{AsCl} \\ \diagup \quad \diagdown \\ \text{NH} \end{array} \text{C}_6\text{H}_4$	193	410
Diphenylcyanoarsine ...	$(\text{C}_6\text{H}_5)_2\text{AsCN}$	35	346

As these substances are used in the form of fine particles and are very stable chemically, some mode of filtering the contaminated air must be used. The effect produced is severe, and recovery is not immediate after withdrawal from the influence of their action.

Treatment. Pain may be alleviated by inhalation of chloroform, and pastilles of glycerin or menthol may afford relief. Rest, fresh air, and a light diet are, however, the best aids to a speedy recovery.

Lachrymators

	Formula	M.p. °C.	B.p. °C.	Antidote
Acrolein ...	$\text{CH}_2=\text{CH}\cdot\text{CHO}$	-88	51	Alkalis
Benzyl bromide ...	$\text{C}_6\text{H}_5\text{CH}_2\text{Br}$	-4	198	S in NaOH
Bromobenzyl cyanide	$\text{C}_6\text{H}_5\text{CHBrCN}$	29	232	Alkalis
Chloroacetone ...	$\text{CH}_3\text{COCH}_2\text{Cl}$		193	Alkalis
Bromoacetone ...	$\text{CH}_3\text{COCH}_2\text{Br}$	-54	136	} $\text{NaBrO} + \text{Na}_2\text{CO}_3$ NaOH in glycerin
Ethyliodoacetate ...	$\text{CH}_2\text{I}\cdot\text{COOC}_2\text{H}_5$		150	
Xylyl bromide ...	$\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\text{Br}$		218	Alkalis
Chloroacetophenone	$\text{C}_6\text{H}_5\text{COCH}_2\text{Cl}$			

It will be seen that these substances vary from liquids with low boiling points to solids. Ethyliodoacetate is semi-persistent and is easily dispersed in bombs or shells. Chloroacetophenone is a solid which may be dispersed in a similar manner to the toxic arsenical smokes.

In small concentrations they cause the eye to water and as the concentration increases this may be accompanied by smarting and pain. In high concentrations the throat and chest may be affected and vomiting ensue. Cases are characterised by the rapidity with which recovery occurs after removal of victims from affected areas. Little treatment is required beyond simple bathing of the eyes.

Direct Poisons. The most important member of this class is hydrocyanic acid, the toxic effects of which are well known and characterised by the rapidity with which death ensues. Professor Barcroft has shown that concentrations of 1 part in 10,000 have little effect and that five times this strength would have been obtained before it could be dangerous. Any treatment must be immediate to be effective; fresh air, artificial respiration and stimulation by massage of the limbs.

Mixtures. The problem is often complicated by the fact that mixtures of various agents are used (see Thorpe, p. 282). This is illustrated by the following list of mixtures which have been used in warfare.

Bromoacetone	80;	Chloroacetone	20						
Chlorine	50;	Phosgene	50						
Chlorine	70;	Chloropicrin	30						
Hydrogen sulphide	35;	"	65						
Stannic chloride	20;	"	80						
Phosgene	25;	"	75						
Hydrocyanic acid	55;	Chloroform	25;	Arsenic chloride	20				
"	50;	"	5;	"	"	30;	Stannic		
Phosgene	50;	Arsenic chloride	50				chloride	15	
Phosgene	60;	Stannic chloride	40						
Trichloromethylchloroformate	65;	Chloropicrin	35						
Trichloromethylchloroformate	with phosgene and diphenylarsine.								
Dichlorodiethyl sulphide	80 with chlorobenzene and carbon tetrachloride.								
Ethyliodoacetate	75;	Alcohol	25						
Ethylchloroarsine	80;	Dichloromethylether	20						

GASES NOT MET WITH IN WARFARE

Carbon Monoxide. This gas occurs when any organic matter is burnt in a restricted amount of air and hence is a component of town gas (6% to 9%) and the exhaust gases of motor engines. It is also one of the components in producer or water gas (25% to 50%) and carburetted water gas (30%). It is colourless, odourless and non-irritant and herein lies its chief danger, since often the first warning of its presence may be inability to move. Its poisonous action is due to its power of combining with the hæmoglobin of the blood, forming a compound which is not decomposed by oxygen. Its affinity for hæmoglobin is about 250 times that of oxygen, and hence in the presence of both gases the partition of the hæmoglobin is strongly in favour of combination with carbon monoxide. Thus, as the absorption of carbon monoxide by the blood proceeds the supply of oxygen to the blood progressively decreases.

Treatment. The first requirements are fresh air, warmth, and complete rest, the latter to reduce the body's demand for oxygen. Administration of pure oxygen is also essential for periods up to

1 hour, sometimes accompanied by artificial respiration. Treatment with air containing 3% to 7% of carbon dioxide has been found beneficial, as the respiratory centre is stimulated with consequent increase in depth and rate of breathing.

Nitrous Fumes. The results of even short exposure to nitrous fumes are sometimes serious, and therefore air which smells slightly of these substances is dangerous. The first symptoms are transitory and consist of irritation of the nose and throat, cough, headache, smarting of the eyes, and vomiting. After a delayed period of from 10 to 20 hours the more serious effects of acute pulmonary congestion and œdema set in. This "delayed action" is a source of danger.

Treatment. Oxygen administration and venesection.

Sulphuretted Hydrogen. This gas is formed when organic matter decomposes. It causes fatalities in sewers, occurs in mines, and is an ever-present danger in certain chemical processes. If concentrated it may resemble carbon monoxide in rapidity of action, the subject appearing to drop almost instantaneously. When in sufficient concentration to asphyxiate, the gas is odourless and is only detected by a sweet taste. It is considered one of the most toxic of gases. Comparable to hydrogen cyanide in rapidity of action, and concentration results in death. Even in concentration of 0.005% the gas is toxic.—*Lancet*, i/1924, 347.

Arseniuretted Hydrogen, AsH_3 . The gas is occasionally encountered in industry and is sometimes evolved from electric batteries as a result of the use of impure materials. The effect is cumulative and is nearly proportional to the product of concentration and time of exposure. It acts upon the red blood corpuscles, producing progressively jaundice, hæmoglobinuria and secondary anæmia, vomiting, fainting, collapse and acute nephritis. Death appears to be due to lack of oxygen caused by the destruction of the red blood corpuscles.

Ammonia. This gas affects the respiratory passages, eyes and skin, effects being proportional to concentration. Immediate removal from the fumes is essential. A pad soaked in dilute acetic acid and applied to mouth and nose will afford relief, and the eyes derive benefit from bathing with boric acid solution.

DEFENCE AGAINST GAS

The early gas masks consisted of helmets soaked in sodium thio-sulphate, with or without sodium carbonate and glycerin. After the use of phosgene the "P.H." helmet, soaked in sodium phenate and hexamine, appeared and also afforded protection against hydrocyanic acid. The extended use of chemical warfare and the multiplicity of the agents used called for different methods of defence, and the helmets gave place to the box-respirator.

The box-respirator consists of a mask provided with goggles which makes an air-tight fit over the face and contains a breathing-tube which connects with the air through a cannister containing absorbent material. The cannister contains mainly three different layers—(a) activated charcoal as a general absorbent; (b) granules composed of antidotes to special gases; (c) a filtering medium to arrest the firm particles of toxic smokes. It is obvious that the composition of the granules can be altered to suit special purposes. That used during the war contained alkaline granules (soda lime and potassium permanganate), containing 15% to 25% of water, which enhanced the catalytic decomposition of some of the gases used. It afforded no protection against carbon monoxide. "Hypocalite," a mixture of copper and manganese oxides, is used for CO but the air must then first pass through a drying agent. A commercial adaptation is illustrated by the use of granules composed of pumice soaked in copper sulphate as a protection against ammonia.

There is no adequate protection against the vesicants, since oil-skin garments or clothes impregnated with chloramine may only be worn for short periods, and the effectiveness of ointments is very doubtful. Rooms may be at least partially protected by covering the openings with curtains impregnated with a heavy mineral or vegetable oil. Special rooms supplied with air-purifying plant could, of course, be provided in advance.

The **decontamination** of areas affected with persistent or semi-persistent gases is difficult—water, earth or a mixture of bleaching powder 1 and sand 3 are the only agents available. The best method for the decontamination of clothing is the use of steam.

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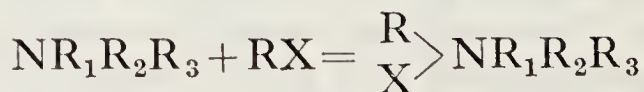
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CHEMOTHERAPY

The Relation between Chemical Constitution and Physiological Effect

The middle of the nineteenth century was a period of great activity in the determination of the constitution of the active principles of many vegetable drugs. One of the most important characters of such substances is their physiological action and, naturally, attempts were made to relate such activity to the chemical constitution of the molecule. Thus the science of chemotherapy came into being. Probably the first successful generalisation in this field was that of Crum Brown and Fraser (*Proc. roy. Soc. Edinb.*, 1867, 560). They showed that various alkaloids, possessing the most diverse physiological actions, on combination with alkyl halides to form quaternary ammonium derivatives,



where $\text{R}_1\text{R}_2\text{R}_3$ are organic radicles of any complexity and RX stands for alkyl halide, methyl or ethyl iodide, etc., yield substances in almost every case possessing the property of paralysing the motor nerve-endings in the same way as curare. One can obtain, therefore, by methylation of all tertiary bases, quaternary ammonium compounds which are poisonous compared with the original bases. Curare itself contains the tertiary base curine which is not very poisonous, as well as the far more poisonous ammonium base curarine. Curine on methylation yields curarine which is 226 times as poisonous as the original substance. This early success stimulated the hope that it would be possible to correlate physiological action with chemical constitution.

Theories of Physiological Action. One of the earliest general hypotheses was that of Loew (*Natürlichs System der Giftwirkung*, Munich, 1893) who held that all substances which react with aldehydes or amines, either by addition or substitution, must possess physiological activity. According to him the greater the reactivity the greater the physiological result, e.g., phenylhydrazine and hydroxylamine are very reactive to ketone and aldehyde groups,—hence poisonous both to plants and animals. Aniline is less reactive to aldehydes than phenylhydrazine and is less poisonous than the latter. If the chemical properties of a substance are made more labile by a change in the character of the molecule, then it becomes more toxic, and vice versa, e.g., if the hydrogen of the NH group in many alkaloids be replaced by a methyl group the toxicity is diminished since the substance reacts less readily with aldehydes. Similarly piperidine is more toxic than pyridine, and tetrahydroquinoline is far more toxic than quinoline by reason of the fact that the reduced compounds which contain secondary nitrogen in place of tertiary have a greater reactivity with protoplasm. Compare also pyrogallol (trihydroxybenzene) which is more poisonous than dihydroxybenzene (catechol) and phenol. The toxicity of phenols is, in the light of this theory, attributed to their reactivity,—especially with aldehyde. Salicylic acid (introduction of COOH) is less reactive with aldehydes than phenol, hence less toxic. Loew's theory is restricted to those substances which react with aldehyde and amino-groups and offers no explanation for selective action. As every tissue contains such groups, all drugs should possess a general activity.

Ehrlich (*Proc. roy. Soc.*, 1900, 424; *Studies on Immunity*, 1906, pp. 404-442) suggested a parallel between the action of a drug and the process of dyeing. Witts' theory of dyeing postulates the presence of a chromophore and a salt-forming group in the dye and, by analogy, the drug must contain a "pharmacophore" and an anchoring group. Thus, by changing the type of anchoring group, the seat of action may be moved and the physiological property of the drug altered. In morphine, the anchoring group may be one, or both, of the hydroxyls and the protection of these by the entrance of an organic radicle, methyl, ethyl, or acetyl, causes the hypnotic power to be reduced whilst action on the respiratory centres (produced by morphine to a slight extent) is much increased, e.g., codeine and diamorphine. Again, benzoylecgonine is twenty times less toxic than its methyl ester (cocaine). It is only necessary for benzoylecgonine to be esterified—the alcohol used is comparatively unimportant—for the typical action of cocaine to appear, and thus it may be that the anchoring group responsible for the local anæsthetic action does not become operative until the carboxyl is masked.

Although these views have not been borne out entirely by subsequent work, they have proved very stimulating to research and have therefore served a useful purpose. One of the main

difficulties with such a theory is that it does not explain the varying activity of compounds containing the same groupings differing only in their orientation.

It has been suggested that such difficulties may be met by substituting a theory of *indirect* action. Thus, bactericides may function by stimulating the formation of antibodies in the host. If this were true the substances should be able to promote immunisation, but as yet no evidence in support has been obtained.

Voegtlin (*Physiol. Rev.*, 1925, 63) has suggested that the activity of the arsenicals is due to their reduction to arsine oxide derivatives which then react with the reduced glutathione present in the tissues. But again the selective action of isomers is not explained.

Effect of Stereoisomerism. Fischer's famous "lock and key" simile has been invoked to explain the well-known differences in compounds related stereochemically. Sometimes the character as well as the potency, of the reaction is different, e.g. *l*-hyoscyamine and *d*-hyoscyamine. Difference in potency is best illustrated by *l*-adrenaline which is about fifteen times as active as its enantiomorph. Again *cis* and *trans* dichlorethylenes show considerable differences in physiological behaviour. The characteristic action of the quaternary ammonium compounds does not appear to be dependent upon the presence of nitrogen as it is exhibited by the S, P, and As analogues. Such substances have one common characteristic—the tri-dimensional form of their molecules.

Physical Factors. Many chemically inert substances possess hypnotic properties. There appear to be few chemical relationships between paraldehyde, chloral hydrate, sulphonal, urethanes, and ureides, and hence Overton and Meyer independently suggested that similar physical properties were responsible for the physiological action of bodies belonging to such different common chemical types. They proved that it was possible to obtain approximately the relative potencies of hypnotics by studying the partition coefficients between olive oil and water. Meyer compared partition coefficients with the fraction of the molecular weight required to produce immobility, and obtained the following results:—

Substance	Partition Coefficient (olive oil : water)	Molecular amount to produce immobility
Methylsulphonal	4.4	0.0013
Tetronal	4.0	0.0018
Sulphonal	1.1	0.006
Bromal hydrate	0.7	0.006
Chloral hydrate	0.2	0.002
Ethyl urethane	0.14	0.04
Alcohol	0.03	0.5

It will be seen that the two methods classify the substances in approximately the same order.

Such a theory accords with the fact that the nerves are surrounded by lipid matter which would protect the nerve fibres from substances insoluble in lipoids. On the other hand, the theory does not explain the action of the drug on the nerve fibre itself or the specificity of the action of certain identities.

The physical properties of a drug and its chemical stability may determine whether the substance can reach the required seat of action without suffering decomposition or general absorption, but it is unlikely that such properties offer a complete explanation for the physiological activity.

Metabolic Reactions. The ultimate fate of the drug in the body is bound to have an effect upon its activity. In general, the changes which occur lead to the production of a less toxic compound by way of hydrolysis, oxidation, or reduction, sometimes followed by the combination of the product with sulphuric, glycuronic, or aminoacetic acid. Hydrolysis takes place in the alimentary tract. The saliva usually has little action; salts of organic acids are generally decomposed into the free acid and a chloride of the base, but esters and similar bodies are in the majority of cases undecomposed by the gastric contents. In the small intestine, however, the drug encounters the pancreatic enzyme, trypsin, and an alkaline medium. Trypsin has marked hydrolysing action on esters, anilides, and similar bodies,—here, after saponification, the components of the drug exert their specific action. Oxidation and reduction occur in the tissues and in the blood. Aliphatic substances are often completely oxidised to carbon dioxide, water, and urea although the methyl group appears to offer considerable resistance. For instance, acetone is oxidised with difficulty, diethylketone easily, whilst methylethylketone occupies an intermediate position. Primary and secondary alcohols are easily decomposed, whilst tertiary alcohols and chloro-derivatives are comparatively resistant.

Aromatic substances are more stable and the nucleus usually remains intact: side chains are converted into carboxyl groups (toluene gives benzoic acid) whilst other substances are transformed into the *para*-hydroxyl derivative. Aniline yields *p*-aminophenol, and this fact accounts for the introduction of derivatives of this compound into medicine, phenacetin being a well-established example. An interesting action of demethylation occurs in the case of xanthine, theobromine and caffeine, the first being without action on the heart muscle, the second acting slightly and the third showing more marked toxic action. It was found that the products of metabolism after giving caffeine and theobromine contain xanthine bases poorer in methyl groups than the substances given. In man, caffeine is reduced to theophylline,—this shows that there is a splitting off of methyl groups, which groups appear to be responsible for action on the heart, i.e., there is a

relationship between physiological action and the changes undergone by the substance in the organism. Reduction occurs much more rarely—quinone forms hydroquinone and certain substituted nitro-compounds are reduced to the corresponding amino-compounds although nitrobenzene is not converted into aniline.

It has been mentioned that products of these reactions are often eliminated in combination with certain acids.

Phenols form the potassium sulphuric esters unless the phenol is relatively non-toxic when it is eliminated unchanged. Methyl salicylate combines with sulphuric acid, but salicylic acid, owing to the presence of the carboxyl group, forms the ester with aminoacetic acid. Aliphatic compounds eliminated with glucuronic acid, $\text{CHO}(\text{CHOH})_4\cdot\text{COOH}$, probably react with glucose to form a glucoside which is then oxidised to the glycuronic acid derivative. Aromatic compounds form an additive compound with the aldehyde group of this acid. The condensation with aminoacetic acid can be illustrated by the formation of hippuric acid:—

$\text{C}_6\text{H}_5\cdot\text{COOH} + \text{NH}_2\text{CH}_2\cdot\text{COOH} \longrightarrow \text{C}_6\text{H}_5\text{CO}\cdot\text{NH}\cdot\text{CH}_2\cdot\text{COOH}$
Thus, benzoic acid, derivatives of benzoic acid, and similar substances formed by oxidation are eliminated as hippuric acid and its derivatives.

From the above survey it is apparent that no one theory explains satisfactorily physiological action, and few generalisations can be made. In fact the original finding of Crum Brown concerning quaternary ammonium compounds still remains almost unique. Other fairly well-established generalisations may include (a) benzoylation of amino-alcohols always gives rise to local anaesthetics; sometimes the use of the *p*-aminobenzoic derivative is preferable as in procaine; (b) the β -position in arylaliphatic amines (e.g. β -phenylethylamine derivatives) appears to be of importance in sympathomimetic compounds; (c) the ethyl group is important in certain classes of hypnotics; (d) the introduction of strong acidic groups such as the carboxyl and sulphonic acid group greatly reduces toxicity and activity. Acylation of amines produces the same effect.

In addition to these few generalisations, a vast amount of information has been obtained, but the findings are applicable only to the series concerned. However, the following summary of the effects of common groupings may serve to illustrate the type of knowledge available.

Inorganic Substances. Blake, in 1839, stated that any activity was due to the electro-positive radicle, acid groupings being inactive. In 1881 it was stated that activity increased with increase of atomic weight amongst isomorphous substances—e.g. Li, Na, K, Rb, Cs, Ag and Tl; Mg, Mn, Co, Ni, Cu, Zn, Cd; Ca, Sr, Ba. Potassium and ammonium provide exceptions but these are also exceptions to Mitscherlich's law of isomorphous substances possessing similar spectra.

Amongst the electro-negative elements there appears to be no relation between activity and atomic weight. The effect appears

to be due to the ions and hence ionisation plays an important part: mercuric cyanide is soluble but little ionised and is much less poisonous than mercuric chloride. Phosphonium, arsonium and stibonium bases exhibit no reactions of P, As, or Sb but resemble the corresponding nitrogen compounds.

Organic Substances. Aliphatic compounds mainly produce hypnotics and aromatic compounds antipyretics.

Schmiedeberg's Rules (*Arch. exp. Path. Pharmac.*, 1886, 20, 201) regarding action of aliphatic compounds. The action of these depends on *volatility and solubility*, *cf.*, the lower with the higher members of the series of paraffins.

(1) Poisonous radicles on substitution by simple alkyl groups lose in intensity, e.g. *arsenious oxide*, $\text{O}=\text{As}-\text{O}-\text{As}=\text{O}$ and *cacodyl oxide*, $(\text{CH}_3)_2\text{As}-\text{O}-\text{As}(\text{CH}_3)_2$.

(2) The effect of the alkyl groups can, on the other hand, be lost or lessened by combining with other atoms or groups, e.g., the mono-, di-, and tri-methylamines behave like ammonia and have no narcotic action, but the first rule holds since these amines are less toxic than ammonia.

(3) The action of a body made by *uniting two groups* by an oxygen atom depends on the two components each acting separately. Where the two groups are similar or equivalent alkyl groups, e.g., in the simple and compound ethers, then the action of the whole is simple and the resulting body resembles in action the corresponding alcohol. Analogous are the esters, the acids of which yield neutral (sodium) salts without any specific physiological action. Acetic ester and its homologues are therefore classed with the alcohols. If the acid, however, has a specific action of its own then this shows itself in the ester, and has a modifying effect on the action of the alkyl group, e.g., amyl nitrite.

Hydrocarbons. Aliphatic hydrocarbons which exhibit volatility and solubility are narcotic, the activity reaching a maximum at C_6 and C_7 . Activity is increased on the introduction of a double bond. Amongst aromatic hydrocarbons benzene compounds show a paralysing action on the motor nerves and a further effect on the brain and spinal cord. Naphthalene is less toxic than benzene.

Effect of Alkyl Groups. In homologous series of compounds produced by varying alkyl radicles, peaks of activity occur—not always at the same point. The ethyl group appears to be particularly effective in hypnotics as illustrated by the sulphones. More generally the peak occurs with the butyl or amyl member.

In derivatives of barbituric acid the two substituent groups on the 5-carbon atom should together contain not less than 4 or more than 8 carbon atoms, and at least one of the groups should be aliphatic. Outside these limits derivatives are either too toxic or too inactive for use.

Replacement of hydrogen of the nucleus by methyl produces

an increase in the effects, *cf.* also the methylation of xanthine (*antea*). Replacement of the hydrogen of a hydroxyl group often reduces activity, *cf.*, catechol, $C_6H_4(OH)_2(1:2)$, guaiacol, $C_6H_4OH \cdot OCH_3$, and veratrole, $C_6H_4(OCH_3)_2$. Again *ortho*-methoxybenzoic acid, $C_6H_4OCH_3 \cdot COOH$, and anisic acid, $CH_3O \cdot C_6H_4 \cdot COOH$, are less active than salicylic acid, $C_6H_4OH \cdot COOH$, but this is not invariably true—resorcinol, $C_6H_4(OH)_2(1:3)$, is far less poisonous than dimethyl-resorcinol, $C_6H_4(OCH_3)_2(1:3)$.

Alkylation of amines reduces toxicity. Some interesting cases of specificity occur: for instance, certain dyes containing the diethylamino group stain nerve fibres whereas the corresponding methyl derivatives are inactive (Ehrlich and Michaelis); *p*-phenyltolcarbamide, $C_2H_5O \cdot C_6H_4 \cdot NH \cdot CO \cdot NH_2$ (dulcin), is intensely sweet whilst the methyl analogue is tasteless. No general rule can be postulated concerning the introduction of the phenyl group.

Effect of Hydroxyl Groups. Depends upon the function which it performs.

Alcohols. Narcotic action reaches a maximum at C_8 , and activity increases with the branching of the chain: secondary are more active than primary, tertiary than secondary; e.g. amylene hydrate. Introduction of further hydroxyls reduces activity, the effect being roughly proportional to the number present. Solubility in water increases as does the property of sweetness, viz. monohydric alcohols, glycols, glycerol, mannitol, etc.

Phenols. Introduction of $-OH$ into the aromatic nucleus increases activity and often promotes antiseptic qualities. Amongst the homologues of phenol increase in molecular weight is accompanied by increased activity and reduced toxicity. Polyhydroxyphenols are still more active and the meta compounds are least active: phoroglucinol is the least active of all the di- and trihydroxybenzenes. Alkyl resorcinols are stronger bactericides than resorcinol, the peak being reached with 4-hexylresorcinol.

Effect of Halogens. In aliphatic bodies there is increase in narcotic power, but there is also an increase in depressant action on the heart and blood vessels. The narcotic power and toxicity of chlorine compounds is well seen in the case of the chlorhydrins, narcotics and vasodilators derived from glycerin which is inert, tri-chlorhydrin being most active and the mono-compound least. Note that in the case of the tri- and mono-chloroacetic acids the toxicity is reversed. Halogen introduced in the benzene nucleus causes little alteration in properties. Organic iodine compounds differ from those of chlorine and bromine in having greater antiseptic and toxic properties and diminished hypnotic effects, *cf.*, $CHCl_3$, $CHBr_3$, CHI_3 .

Although the entrance of halogens increases the narcotic action of a drug the molecule acts as a whole, neither chlorine nor bromine being set free in the tissues. Examples: chloral hydrate, chlorbutol.—J. Grier, *Brit. colon. Drug* i/1913, 282.

Aldehydes. Formaldehyde is very reactive chemically and physiologically. It is a strong irritant to the mucous membrane and coagulates proteins. Acetaldehyde produces excitation and then anæsthesia. Paraldehyde is stronger in action than the latter. By entry of OH into the aldehyde molecule and by condensation of these bodies to form aldols, reactivity is lowered, as also physiological power,—the sugars are practically inert. The aromatic aldehydes are of low toxicity.

Ketones. Similar to alcohols—narcotic. Hypnotic action is seen in the mixed ketones, e.g., acetophenone, $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CH}_3$.

Effect of Acid Groups. The introduction of such groupings usually increases considerably the solubility and therefore the “dispersibility” of a compound. Hence they cause generally a decrease in activity or total suppression, e.g., substances containing an OH group, on combining with sulphuric acid, lose their toxicity—phenol is toxic but phenylsulphuric acid is harmless, *cf.*, also morphine, $\text{C}_{17}\text{H}_{17}\text{NO}(\text{OH})_2$, and morphine-sulphuric acid, $\text{C}_{17}\text{H}_{17}\text{NO}(\text{OH})\cdot\text{O}\cdot\text{SO}_2\cdot\text{OH}$ —this latter is practically inert. The sulphonic acids of various drugs are in nearly every case of little use; the introduction of carboxyl (COOH) is almost analogous. COOH , for example, reduces toxicity of benzene, which can be taken in doses of 8 g. per day in comparison with a dose of 12 g. to 16 g. of benzoic acid. Methylamine, NH_2CH_3 , is toxic; glycine, $\text{NH}_2\text{CH}_2\cdot\text{COOH}$, is harmless. If the carbo-methoxy group in cocaine be hydrolysed there is a total loss of activity which is regained on esterification.

Acylation of amino groups—i.e. the introduction of an acid residue—has a similar effect on toxicity. The base is liberated slowly by hydrolysis and thus the action is retarded and the concentration of the base remains below the toxic limit. The acetyl group is most generally used but the lactyl, benzoyl and salicyl are not uncommon. Practically all synthetic antipyretic and analgesic drugs contain the acetyl radicle. Not only so but it occurs in such naturally occurring pain-relieving drug-principles as aconitine and colchicine.

Effect of Nitro and Nitroso Groups. Replacement of the hydrogen of the hydroxyl-group by the nitro- and nitroso- groups yields the nitrates and nitrites respectively. Both these classes of substances are vasodilators. Peak of activity is obtained at C_5 (amyl nitrite), the nitrites of secondary and tertiary alcohols being stronger than those of primary. Glyceryl trinitrate and erythritol tetranitrate are examples of nitrates used for the same purpose.

Introduction of the nitro- group into aromatic compounds invariably increases toxicity and is not accompanied by any action of dilatation.

Effect of the CN Radicle. Isocyanides (isonitriles) cause paralysis of the respiratory centre and the cyanides (nitriles) produce coma. Neither, however, are as poisonous as HCN . The

lower members in the fatty series, CH_3CN and $\text{C}_2\text{H}_5\text{CN}$, are less poisonous than the higher—cyanacetic acid, $\text{CNCH}_2\cdot\text{COOH}$, practically non-toxic. Cyanogen chloride, CNCl , on the other hand, is very toxic as it yields readily HCN .

Effect of Basic Nitrogen Groups. These can produce either series important changes. The introduction of alkyl groupings into such bodies increases basicity and reduces toxicity and as before gives hypnotic effect, e.g., carbamic acid, NH_2COOH (poisonous), gives urethane (ethyl carbamate)—more stable and hypnotic. Hydrazine, $\text{NH}_2\text{—NH}_2$, is far more toxic than NH_3 but the tetra- and penta-methylenediamines are non-toxic.

The entry of the amino group into the benzene nucleus forms the groundwork of a large number of antipyretics and analgesics. The aromatic amines are less basic than ammonia. Aniline, like ammonia, produces convulsions, but like benzene it also causes paralysis of muscles and nerves, and if one of the hydrogen atoms of the NH_2 group be replaced by alkyl the convulsions disappear but the paralysing action remains. If a hydrogen atom in the nucleus be replaced by a single atom, e.g., Br, the convulsant effect is retained, and if it is replaced by an alkyl group the effect is increased, but if a complex group, especially an acid group, e.g., SO_3H , enters the nucleus, the effect is lost, e.g., in aminobenzenesulphonic acid, $\text{C}_6\text{H}_4\cdot\text{NH}_2\cdot\text{SO}_3\text{H}$. All these derivatives, e.g., aniline, have a toxic action on the blood, forming methæmoglobin. As a rule, aromatic derivatives of NH_3 lower temperature.

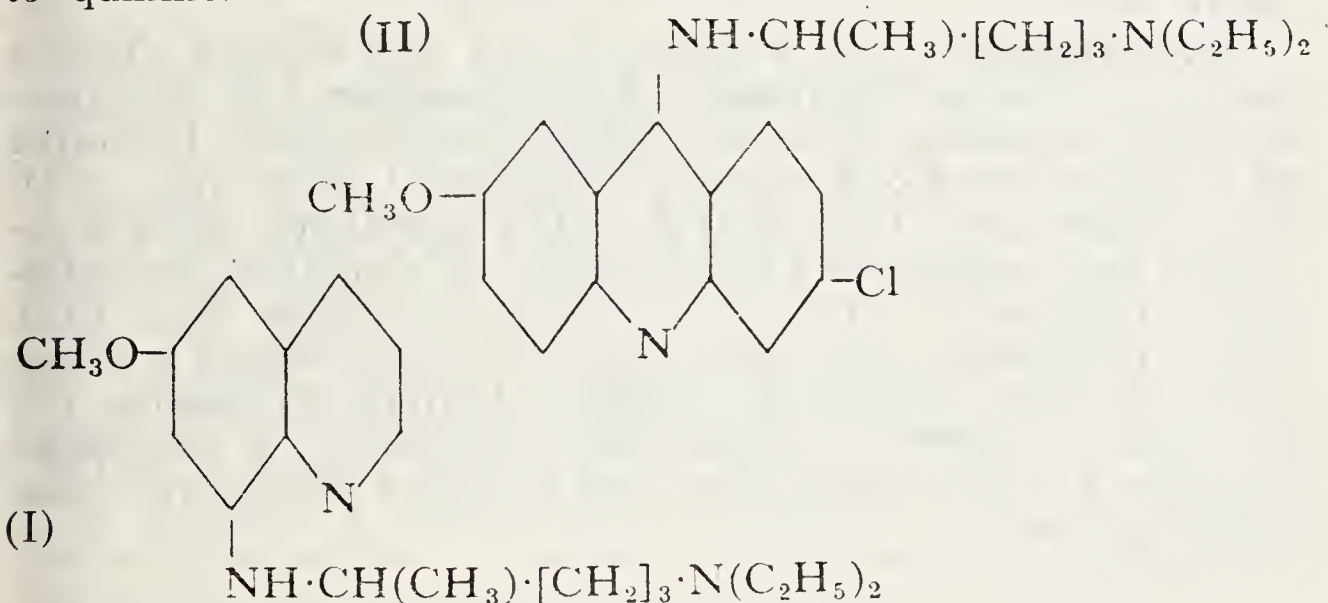
Alkaloids (see also J. A. Aeschlimann, *J. Soc. chem. Ind. Lond.*, 1935, 136T).

No general clue to physiological effects is possible since in most cases the whole molecule appears to be essential. Most alkaloids possess valuable and potent physiological actions often accompanied by dangerous and unwanted side effects, as witness the habit-forming characteristics of morphine and cocaine. For this reason the efforts to synthesise compounds retaining the physiological effect of many alkaloids, but without the unwanted reactions, have not only contributed new and important drugs but have been instrumental in widening the boundaries of knowledge in chemotherapy. The following summary contains many of the recent introductions of synthetic "chemical improvements" of certain alkaloids which have been produced by work along these lines.

Cocaine. The study of the cocaine molecule has been responsible for the production of many local anæsthetics of which the eucaines were the first examples and procaine (Novocain) the most successful. Recently the introduction of Tutocain (1927, *p*-aminobenzoyl ester of γ -dimethylamino- $\alpha\beta$ -dimethylpropyl alcohol), and Larocain (1930, *p*-aminobenzoyl ester of γ -diethylamino- $\beta\beta$ -dimethylpropyl alcohol) illustrate improvements obtained by using alcohols of higher molecular weight with a more branched chain containing the amino-group in the γ -position.

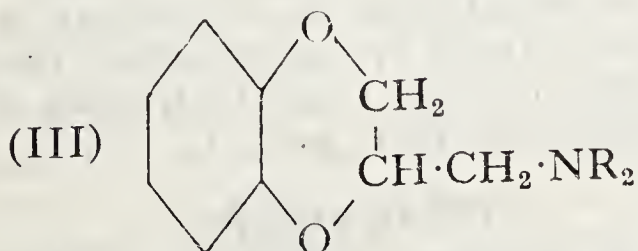
Pantocain (1931, N-*n*-butyl derivative of procaine) is eight times as active as cocaine but more toxic, and shows the effect produced by modification of the aromatic amino group of procaine.

Quinine. This alkaloid has both antipyretic and antimalarial activity. The first synthetic antimalarial was Plasmoquin (I), introduced in 1927, which acts at a different stage in the life history of the parasite from quinine. Atebrin (II) acts similarly to quinine.

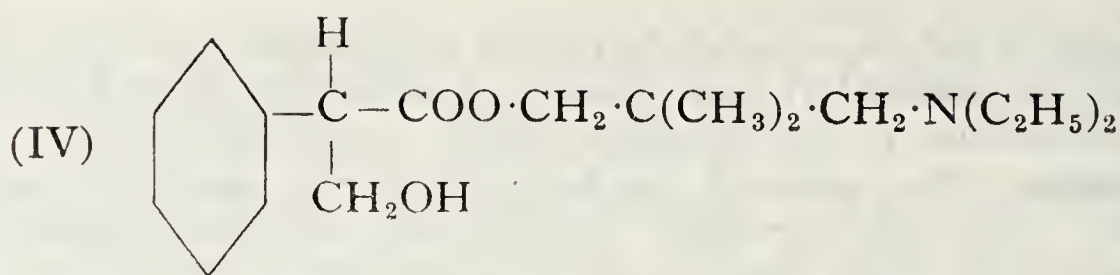


A large number of compounds similar to the above types have been produced in recent years (Pyman, *Chem. Ind. Rev.*, 1930, 758; Kernack, *J. chem. Soc.*, 1931, 3089; Mike and Robinson, *J. chem. Soc.*, 1933, 1467; Madison and Strukow, *Arch. Pharm., Berl.*, 1933, 271, 359; 1934, 272, 74) from which it appears that the 6-hydroxy-derivative instead of the alkoxy-derivatives are worthy of attention.

Ergot Alkaloids. The constitution of the ergot alkaloids still remains unknown, and the problem becomes ever wider by the isolation of new alkaloids. However, Fourneau and collaborators have found that the benzodioxan derivative (III) possesses many of the characteristic actions of the ergot alkaloids.

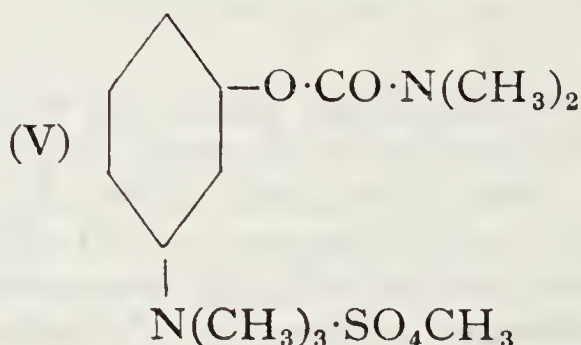


Atropine. Tropic esters of amino-alcohols simpler than tropine are found to possess antispasmodic properties. Syntropan (IV) (Fromhery, *Arch. exp. Path. Pharmacol.*, 1933, 173, 86) shows great promise, and it is claimed that the antispasmodic action is greater, whilst the mydriatic action is weaker than atropine and that it does not interfere to such an extent with the secretory functions.



The *l*-tropic ester is again much stronger than the optical enantiomorph.

Physostigmine. This substance is the only alkaloid which is used as an injectable peristaltic, but it possesses two important unwanted properties: it is very unstable and too toxic. Following the diagnostic work of Barger and Stedman (*J. chem. Soc.*, 1922, 891; *J. chem. Soc.*, 1923, 759) the latter contributor and his co-workers have synthesised a large number of "simplified physostigmines" (*Biochem. J.*, 1926, 719; 1929, 17; *J. chem. Soc.*, 1929, 609; *J. Pharmacol.*, 1931, 259), all of which possessed a miotic action and were unstable in solution. Latterly Prostigmin (Tropicarb) (see *Lancet*, i/1934, 942) has been introduced, a compound which has a stronger peristaltic with a smaller miotic effect than physostigmine.



An interesting side-light on the action of this compound received considerable attention recently, due to the use of it and physostigmine in the rare kind of paralysis known as myasthenia gravis (see also *Lancet*, i/1934, 1200; *Brit. med. J.*, 1/1934, 432). At first it was thought that this successful application was due to the anti-curare effect of these compounds—a reaction which is remarkable as Prostigmin is a quaternary compound itself—but latterly it has appeared that the action is due to the prevention of a too rapid hydrolysis of acetylcholine (see *Biochem. J.*, 1932, 56; *Brit. med. J.*, i/1934, 838).

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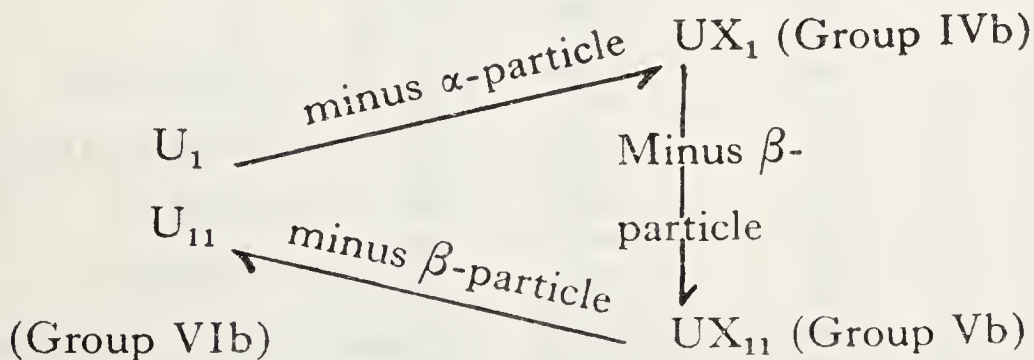
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MODERN VIEWS OF ATOMIC STRUCTURE

The beginning of the end of the conception (Dalton) of the atom as an indivisible unit—a “solid, hard, impenetrable particle” (Newton)—was the discovery of cathode rays by Crookes. The nature of the cathode rays is independent of the source and hence they could be considered as invariable constituents of atoms. Next, the α and β particles emitted by radioactive elements during disintegration were recognised as charged helium atoms and electrons respectively. Rutherford (*J. chem. Soc.*, 1922, 122, 400) has shown that bombardment of Na, B, Al, N, P, and F with α particles liberated charged hydrogen atoms. Thus the composite character of the atom was recognised and the idea that all atoms were composed of three entities—hydrogen nuclei, helium nuclei and electrons—arose. Since the atom is electrically neutral the numbers of protons (hydrogen nuclei) and electrons must be equal. The protons and helium nuclei are situated in the nucleus and the balance of electrons, required for neutrality, in the sheath. The number of electrons in the sheath equals the difference between the number of protons and electrons in the nucleus and is the fundamental property of the atom called the **Atomic Number**.

Consider the following radioactive change.



The loss of four protons and two electrons (α particle) changes not only the mass of the atom but also the atomic number and, therefore, the periodic group. The further loss of two electrons (β particles) restores the substance to its original atomic number and thus U_1 and U_{11} possess the same atomic number and identical chemical properties but differ by 4 units of mass. Soddy called elements so related **Isotopes**.* The ordinary atomic weights used in chemical analysis are the mean values of the isotopes present, but as this appears to be constant the new conception does not affect quantitative work. Reference to the Table of Isotopes illustrates a further point; different elements may have the same atomic weight, e.g., Ne^{23} and Na^{23} ; Ar^{40} and Ca^{40} ; etc. Such elements are named **Isobares**.

*See *Isotopes*, by F. W. Aston. Arnold & Co., London, 1923.

TABLE OF ISOTOPES AND ATOMIC WEIGHTS

Element	Atomic Number	International Atomic Weight	Isotopes, in order of abundance
H	1	1.0078	1, 2
He	2	4.002	4
Li	3	6.940	7, 6
Be	4	9.02	9, 8
B	5	10.82	11, 10
C	6	12.00	12, 13
N	7	14.008	14, 15
O	8	16.0000	16, 18, 17
F	9	19.00	19
Ne	10	20.183	20, 22, 21, 23
Na	11	22.997	23
Mg	12	24.32	24, 25, 26
Al	13	26.97	27
Si	14	28.06	28, 29, 30
P	15	31.02	31
S	16	32.06	32, 33, 34
Cl	17	35.457	35, 37
Ar	18	39.944	40, 36
K	19	39.096	39, 41
Ca	20	40.08	40, 44
Sc	21	45.10	45
Ti	22	47.90	48
V	23	50.95	51
Cr	24	52.01	52, 53, 50, 54
Mn	25	54.93	55
Fe	26	55.84	56, 54
Co	27	58.94	59
Ni	28	58.69	58, 60
Cu	29	63.57	63, 65
Zn	30	65.38	64, 66, 68, 67, 65, 70, 69
Ga	31	69.72	69, 71
Ge	32	72.60	74, 72, 70, 73, 75, 76, 71, 77
As	33	74.91	75
Se	34	78.96	80, 78, 76, 82, 77, 74
Br	35	79.916	79, 81
Kr	36	83.7	84, 86, 82, 83, 80, 78
Rb	37	85.44	85, 87
Sr	38	87.63	88, 86, 87
Y	39	88.92	89
Zr	40	91.22	90, 94, 92, (96)
Nb(Cb)	41	92.91	93
Mo	42	96.0	98, 96, 95, 92, 94, 100, 97
Ma	43	?	
Ru	44	101.7	102, 101, 100, 99, (98), 96
Rh	45	102.91	
Pd	46	106.7	
Ag	47	107.880	107, 109
Cd	48	112.41	114, 112, 110, 113, 111, 116
In	49	114.76	115
Sn	50	118.70	120, 118, 116, 124, 119, 117, 122, 121, 112, 114, 115
Sb	51	121.76	121, 123
Te	52	127.61	128, 130, 126
I	53	126.92	127
Xe	54	131.3	129, 132, 131, 134, 136, 130, 128, 126, 124
Cs	55	132.91	133
Ba	56	137.36	138, 137, 136, 135
La	57	138.92	139

TABLE OF ISOTOPES AND ATOMIC WEIGHTS—*continued*

Element	Atomic Number	International Atomic Weight	Isotopes, in order of abundance
Ce	58	140.13	140, 142
Pr	59	140.92	141
Nd	60	144.27	142, 144, 146, 145
—	61	—	
Sm	62	150.43	
Eu	63	152.0	
Gd	64	157.3	
Tb	65	159.2	
Dy	66	162.46	
Ho	67	163.5	
Er	68	167.64	
Tm	69	169.4	
Yb	70	173.04	
Lu	71	175.0	
Hf	72	178.6	1
Ta	73	181.4	181
W	74	184.0	184, 186, 182, 183
Re	75	186.31	187, 185
Os	76	191.5	192, 190, 189, 188, 186, 187
Ir	77	193.1	
Pt	78	195.23	
Au	79	197.2	
Hg	80	200.61	202, 200, 199, 201, 198, 204, 196, 197, 203
Tl	81	204.39	205, 203
Pb	82	207.22	208, 206, 207, 204, 209, 203, 208
Bi	83	209.00	
Po	84	210	
—	85	—	
Rn	86	222.00	
—	87	—	
Ra	88	225.97	
Ac	89	?	
Th	90	232.12	
Bu	91	?	
U	92	238.14	238

Periodic Law. Mosely found that the vibration frequency (V) of the principal line in the X-ray spectrum of an element is related to the atomic number (N) by the equation $V = A(N-1)^2$ where A is constant. Thus, a practical method was found for the determination of Atomic Numbers. It was found that arrangement of the elements according to their atomic numbers produced the same sequence as the atomic weights *except* in the case of argon (18) and potassium (19); cobalt (27) and nickel (28); tellurium (52) and iodine (53). Hence arrangement according to atomic numbers agrees perfectly with the chemical properties, and the periodic law can be more accurately stated: "*The properties of the elements are periodic functions of their atomic numbers.*" The way for the reconstruction of the periodic system on a more fundamental basis opened out, and the series suggested by Rydberg (*Zeit. phys. Chem.*, 1897, 14, 66) when corrected in the light of the knowledge of atomic numbers, exhibits a newly found simplicity. Each of the inert gases completes a period of the elements, and the number of elements in each period can be reduced to a simple progression.

	He	Ne	Ar	Kr	Xe	Rn	
	2	10	18	36	54	86	
Atomic number ..	2	10	18	36	54	86	
Number of elements in each period	2	8	8	18	18	32	=
	2[1 ²	2 ²	2 ²	3 ²	3 ²	4 ²]	

The new periodic table constructed according to atomic numbers (*q.v.*) accommodates the rare earths and should be compared with that due to Mendeléeff.

PERIODIC TABLE: ATOMIC WEIGHTS (MENDELÉEFF)

Group 0.	1	2	3	4	5	6	7	8
α								
γ	H 1.0078							
He 4.002	Li 6.94	Be 9.02	B 10.82	C 12.00	N 14.008	O 16.0000	F 19.00	
Ne 20.183	Na 22.997	Mg 24.32	Al 26.97	Si 28.06	P 31.02	S 32.06	Cl 35.437	
A 39.994	K 39.1	Ca 40.08	Sc 45.10	Ti 47.90	V 50.95	Cr 52.01	Mn 54.93	Fe 55.84; Co 58.94; Ni 58.69
	63.57 Cu	65.38 Zn	69.72 Ga	72.60 Ge	74.93 As	79.2 Se	79.916 Br	
Kr 83.7	Rb 85.44	Sr 87.63	Y 88.92	Zr 91.22	Nb 93.3	Mo 96.0	Ma ?	Ru 101.7; Rh 102.91; Pd 106.7
	107.88 Ag	112.41 Cd	114.8 In	118.70 Sn	121.76 Sb	127.5 Te	126.92 I	
X 131.3	Cs 132.81	Ba 137.36	La 138.92	Ce 140.13				
			Yb 173.5		Ta 181.4	W 184.0		Os 190.8; Ir 193.1; Pt 195.23
	197.2 Au	200.61 Hg	204.39 Tl	207.22 Pb	209.00 Bi			
		225.97 Ra		232.12 Th		U 238.4		

In an Appendix to *The Principles of Chemistry*, 1905, Mendeléeff included the elements of the argon group and radium, and found places in addition for two hypothetical elements which he placed before helium and designated α and γ . γ is supposed to be an analogue of helium and may be identified hereafter with "coronium," which has been recognised in the sun's coronal atmosphere. This gas according to Mendeléeff would have density about 0.2 and therefore, molecular weight 0.4 or about $1/10$ that of helium.

α is the "ether" for which Mendeléeff supposes a molecular structure. It is assumed to be inert like the argon group and to possess a low density and atomic weight estimated at 0.000,000,000,053.—Mendeléeff Memorial Lecture.—Tilden, *Nature*, *Lond.*, i/1910, 416.

An element with the atomic weight 3 has been found by J. J. Thomson. An element with this weight had been predicted by Mendeléeff, who endowed it with super-fluorine properties.—*Pharm. J.*, i/1913, 101.

VALENCY

It is now generally accepted that the atoms of the elements all have the same type of structure, consisting of a positively charged central nucleus of minute dimensions, responsible for most of the mass of the atom, surrounded by electrons which occupy, rather than fill, a much larger region. The relative sizes concerned in atomic structure can be better realised if multiplied by a number such as 10^{13} . Thus:—

	Actual	Multiplied by 10^{13}
Diameter of Atom . .	$2-4 \times 10^{-8}$	$1\frac{1}{4}-1\frac{1}{2}$ miles
„ „ Electron	1.88×10^{-13}	1.88 cm.
„ „ Proton	1×10^{-16}	0.01 mm.
„ „ Nucleus	$3-30 \times 10^{-13}$	3—30 cm.

True individuality rests with the nucleus: when altered, transmutation occurs, a change which is difficult to promote and is irreversible. The physical and chemical properties of the elements are decided by the number and arrangement of the external electrons, and these are governed by the nuclear charge, the mass having only a secondary effect.

Physicists differ in their conception of the manner in which the electrons are grouped round the positive nucleus. J. J. Thomson (1904) deduced that electrons would form certain ring systems, according to the number present; the periodic recurrence of similar rings accounting for the periodicity of the properties of the elements.

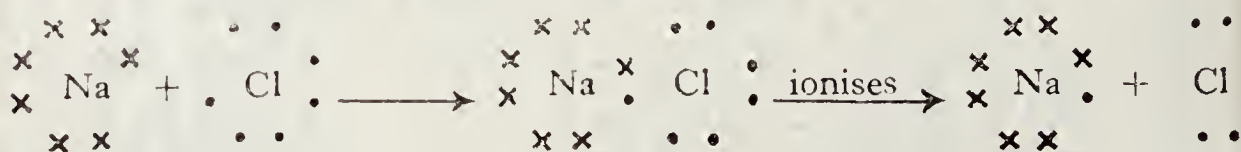
Bohr (1913) also regards the electrons as circulating round a nucleus, but assumes they “jump” from one orbit to another, causing spectra. Four different types of atoms are recognised:—

- All electron groups complete—no compounds formed—inert gases.
- All but the outermost electron group complete: the atoms with fixed valency numbers.
- Two outermost groups incomplete: valency varies by single unit (Fe and Fe^{'''}): the transitional elements.
- Three outermost groups incomplete: long series of elements with the same valency (3) and similar properties—the rare earths.

(For other views *v. Recent Advances Physic. and Inorgan. Chem.*—Stewart.)

Abegg's rule of eight (1904) had the merit of focussing attention upon the relationship between positive and negative valencies. Kossell (1916) related positive valency to the number of electrons an atom must lose, and negative valency to the number of electrons it must gain, to form a stable electronic configuration.

The Langmuir-Lewis Octet Theory differs from the majority in being based on the chemical behaviour of the elements. It is suggested that the external electrons, which determine the valency of the atom, tend in most cases to form “octets,” that is, become arranged in space at the angles of a cube. Two atoms unite to form stable groups of electrons, either by transferring electrons from one atom to another, or else by sharing electrons. In the former case, the atoms are left oppositely charged but held together by electrostatic forces, Na + Cl being an example of electro-valency, whereas in the second case the valency is non-polar, e.g. Cl—Cl, and is called a covalency.



Polar link: electrons transferred: compound ionises.



Non-polar link—covalent link: no ionisation.

	when X = Cl, 7 electrons from Cl	1 from outside, hence $[\text{ClO}_4]'$
	„ X = S, 6 „ „ S	2 from outside, hence $[\text{SO}_4]''$
	„ X = P, 5 „ „ P	3 from outside, hence $[\text{PO}_4]'''$
	„ X = Si, 4 „ „ Si	4 from outside, hence $[\text{SiO}_4]''''$

$$R - N \leq \begin{matrix} 0 \\ 0 \end{matrix}$$
$$\begin{array}{c}
 \text{H} \\
 \times \bullet \\
 \text{H} \times \text{N} \times \\
 \bullet \times \\
 \text{H}
 \end{array}$$
$$\left[\begin{array}{ccccc} & & \text{H} & & \\ & \times & & & \\ \text{H} & \cdot & \text{N} & \times & \text{H} \\ & \times & & & \\ & & \cdot & \times & \\ & & \text{H} & & \end{array} \right]$$

Bibliography. Andredi: *The Structure of the Atom*; Sidgwick: *Atomic Structure and the Periodic Table*; Caven: *Atoms and Molecules*.

RADIUM

Radium was prepared by Madame Curie and M. A. Debierne (1910) in the pure basic condition by electrolysing a solution of a radium salt, using a mercury cathode.

The 25th anniversary of the discovery of radium by M. Pierre Curie and Mme. Curie was celebrated at the Sorbonne on December 26th, 1923. A Bill passed by the French Government granted Mme. Curie a pension of 40,000 francs a year.

Mme. Curie died on July 4th, 1934 (see *Brit. J. Radiol.*, N. S., 1934, 522).

Yield of Radium. Upwards of 0.25 g. of pure radium bromide can be obtained from a ton of pitchblende residue. This approximates statements one finds elsewhere to the effect that pitchblende contains 1 of radium in 5 million parts, or 1 ounce in 150 tons.

Distribution. Although from time to time various pitchblende and other uranium-containing ores have been mentioned as being worth operating for radium both in this country (Cornwall) and abroad, it is stated that at present about 95% of the world's output comes from the uranium ore deposits in the Belgian Congo (Haut Katanga). Uranium ores occur at that locality in conjunction with copper.

Discovery of rich pitchblende ore a few feet below the surface on the shores of the Great Bear lake, about 1100 miles north of Edmonton (Alberta). Development has begun on 4 pitchblende-silver workings, and some 40 tons of high-grade pitchblende-silver ore have been shipped. The pitchblende content of this ore is expected to produce 5 g. of radium. A plant has been constructed at Port Hope, on Lake Toronto. Owing to the absence of impurities such as vanadium and thorium, the treatment is said to be cheaper and faster than that of the Katanga ores and it is believed the general grade will be higher.—*Br. med. J.*, ii/1932, 1024.

The British Radium Corporation deal with pitchblende at Trentwith in Cornwall, but have extracted probably not more than 10 g. of radium.—*W. E. Dixon, Brit. med. J.*, i/1929, 238.

Carnotite, which contains uranium and vanadium, from America and Australia, and **autunite** from Portugal and China, are sources of supply, as is **torbenite**, but these minerals are by no means so rich in radium. Carnotite usually contains the equivalent of about 10 mg. of $\text{RaBr}_2 \cdot 2\text{H}_2\text{O}$ per ton.

Autunite (from Portugal) is comparatively rich in uranium but much contaminated with soil. The ore contains from 1% to $1\frac{1}{2}\%$ of uranium, from one ton of such material about 2 mg. of radium bromide can be produced.

Euxenite, a radioactive mineral in the state of Minas Geraes, Brazil, has been worked for radium.—*Lancet*, i/1922, 260.

Commerce. The radium salt now chiefly in request is the sulphate which is most suitable for the preparation of radium applicators, the chloride and bromide being preferable for emanation purposes. The price of radium rose from £2 to £10 per milligramme in 1904, to £12 in 1906, £27 in 1910, £30 in 1911.

1912, and £36 in 1914; by 1922 it had dropped to £22 per milligramme, with a further fall to £14 in 1923, the price now (1935) being £12. *To the end of 1924 a little over 300 g. of radium had been produced*, of which 120 g. were owned by America.

A large supply of radium for hospital use has been purchased by the Radium Commission set up in 1930. The fund commemorated the recovery of His Majesty King George V. This radium is loaned to various centres under controlled conditions.

The total amount put at the disposal of the Radium Commission by the National Radium Trust is approximately 20 g., of which 18 g. is on loan to centres, the M.R.C. and the N.P.L., and 1·87 g. is allocated to Edinburgh, Leeds, Manchester and Sheffield. The Commission also exercises control over 3 one-gramme units at the Cancer, Middlesex and University College Hospitals, making a total amount of 23 g. under its control. There are now 13 national and 5 regional radium centres, the total quantity of radium available for treatment in the country (including that under the Commission's control) being estimated at 70 g.—*Brit. med. J.*, ii/1934, 780.

The Government of Australia purchased, in 1928, 10 g. of radium at a cost of £100,000, 2 g. being allotted to Sydney, 2 g. to Melbourne, and 0·5 g. each to Brisbane, Adelaide, Perth, and Hobart; 4 g. being kept in reserve.

Hydrated Radium Bromide, $\text{RaBr}_2 \cdot 2\text{H}_2\text{O} = 421\cdot814$, occurs in hard, yellowish, crystalline particles, and is best kept in hermetically-sealed containers so as to exclude moisture.

Characters of Radium. Radium should be placed below barium in the Mendeléeff series, and on the same line as thorium and uranium (*vide* Periodic Table). These three radioactive elements have the highest atomic weights. Radium is divalent. Its spectrum resembles those of the alkaline earths. A freshly prepared radium salt is relatively inactive, as many of the radiations of importance come not from radium itself but from its products. These have not had time to be fully "grown" from the parent substance until about three weeks or so. Radium and its disintegration products emit rays which will be described. See "Atomic Disintegration." Radium decomposes water into hydrogen and oxygen. Oxygen is converted into ozone. It turns glass in its proximity to various colours depending on the composition of the glass. Mercury is converted into the yellow oxide. The rays emitted burn the skin if kept in close proximity for a length of time.

Electrical Properties of Radium. The rays emitted by a highly active preparation discharge a charged gold-leaf electroscope even through an inch or more of iron, zinc or lead—5 milligrammes will do this at a distance of a few yards.

This occurs whether the charge on the leaves be + or —. All the three types of radiation from radium have the effect of ionising air in the electroscope, breaking the molecules into constituent atoms, each of which is electrically charged + or —. These charged particles collide with the charged gold leaves, and such as are of opposite sign to the charge on the leaves neutralise a corresponding amount of electricity on the leaves.

A single atom may be detected by suitable means, using amplifying circuits.

Tests for Purity. Good radium bromide should light up a screen through several copper coins. It should make willow leaves fluoresce. Glew's instrument for estimation of activity consists of an electroscope with ground glass front. A positive charge is given to the leaf by means of a charged camel's hair brush. The time this charge will remain (usually a day or two) is not affected. Markings are made on the ground glass at certain intervals, and on bringing a known weight of pure radium bromide, preferably in a metal box, to within a distance of a yard, the time taken for the leaves to fall is observed. Then if a pure sample causes a drop in 60 seconds it follows that the same weight of another specimen doing the same work in 120 seconds is only 50% pure and so on. In this method the β and γ rays are not measured directly (the α rays do not come in at all) as they do not penetrate the metal box.

A Balance Method for Comparing Quantities of Radium. In making comparisons the best method is to compare the γ ray activities of the specimens. If the radium is enclosed in a sealed tube, the γ ray activity reaches a practical maximum after two months, and the intensity of the penetrating γ rays emitted serves as a definite measure of the quantity of radium. The greater part of the penetrating γ rays are emitted by radium C, and investigations by Moseley and Makower have shown that about 11.5% of the total γ activity is to be ascribed to radium B. The γ rays from the latter are on average much less penetrating than those from radium C, and are completely absorbed by a lead screen 2 cm. thick.

The specimens must contain **no mesothorium or radiothorium**. Both the latter substances emit γ rays of about the same penetrating power as those given out by radium. Since mesothorium and radium are always isolated together, and are chemically closely allied, it is impossible to isolate pure radium compounds from minerals containing both uranium and thorium. The uraninite deposits at Joachimsthal contain only a trace of thorium, so that radium from this ore can be obtained practically free from mesothorium. The electroscope used is surrounded by lead 3 mm. thick.

The primary β rays are completely stopped by the lead and the ionisation in the electroscope is due to the more penetrating γ rays and to the β radiation to which they give rise. The rate of movement of the gold leaf of the electroscope between two fixed points is proportional to the intensity of the γ radiation.—Rutherford and Chadwick, *J. Röntgen Soc.*, July, 1912.

Radium Standard (International). This consists of 21 mg. of radium chloride made by Madame Curie and stored in a thin sealed glass tube at the Bureau des Poids et Mesures, Sèvres, Paris. Another International Standard is kept at the Academy of Sciences at Vienna. Duplicate standards are in the hands of governments of other countries.

The **British Radium Standard** is kept at the National Physical Laboratory, Teddington. It contains about 20 mg. of pure radium chloride. The activity of specimens should be expressed in terms of metallic radium instead of bromide. *It is preferable to prevent misunderstanding regarding the $2\text{H}_2\text{O}$ crystallised radium bromide.* Also the activity is proportional to the number of radium atoms present and is independent of the chemical compounds in which they find themselves.

Standard Solution of Radium. Sealed tubes are made containing 1/100,000 mg. of radium as metal in 10 ml.

In estimating radium in samples of its salts, it is necessary to weigh out a small specimen. The specimen should be dissolved in 100 ml. of water, some pure hydrochloric acid being added; of this 5 ml. should be diluted to 1 litre, making 1 mg. in 20,000 ml. of water, or 1/20,000th of a milligramme in 1 ml. If 1 ml. be diluted to 50 ml. the strength will be approximately that required for the electroscope, and a comparison may be made with the standard. To calculate the radium to pure crystallised bromide multiply by the factor—

$$\frac{421.814}{225.95} = 1.867.$$

The Katanga Company states their preparations are 98% to 99.5% pure—the highest practicable degree of purity obtainable. For suggested Standard for the Emanation *vide* Emanation.

Atomic Disintegration. Radium disintegrates and passes in its change through a series of other bodies.

Uranium and thorium, according to Rutherford, represent the sole survivals to-day of types of elements common when atoms now composing the earth were in course of formation. Owing to their slow rate of transformation some atoms of uranium and thorium have survived—they have not yet completed the cycle of changes which the atoms of other elements have long since passed through.—*J. Röntgen Soc.*, October 1923.

In the case of a radio-element like radium, considered at any instant, among its hosts of atoms, most of which are destined to last for hundreds or thousands of years, a comparatively very small proportion fly apart every second expelling α particles and becoming emanation atoms. Next second a fresh set disintegrates, and so on, α particles being expelled, and yet so small a fraction of the whole changing that the main part of the radium remains unchanged even after hundreds of years.—Soddy.

In the case of the emanation atoms a much larger fraction change per second, producing more α particles, and the active deposit.

The "*Radio-Active Constant*" λ represents the fraction of the total of an element changing per second. For the Emanation $\lambda = \frac{1}{5077700}$. (Rutherford gives 2.085×10^{-6} (seconds) $^{-1}$).

The *Average Life* of an atom, i.e., the time in seconds it exists on the average before its time comes to disintegrate, is the reciprocal $1/\lambda$. In the case of radium emanation the average life is obviously 132.4 hours, or 5.52 days.

The average life of radium is probably about 2,500 years. In other words $\frac{1}{2500}$ part of a given mass of radium changes annually.

The genetic relation between uranium and radium has been established. There is always a definite proportion of radium to uranium present in uranium minerals—for every 1 part of radium there always exist 3,000,000 parts of uranium. $1/\lambda$ for uranium is 8,000,000,000 years (current figure gives 6.75×10^9 , i.e. 6,750,000,000 years). The average life is always 1.443 times the time T known as *the period* required for the quantity of the

element to be diminished to $\frac{1}{2}$ value. Thus the $\frac{1}{2}$ value of radium is 1580 years and $1580 \times 1.443 = 2280$ years, i.e., the average life of radium. For the emanation the average life = $3.85 \text{ days} \times 1.443 = 5.52$ days.

Conversely to find the "*Periods*" or "*Half Values*" from average lives multiply the average lives by $\frac{1000}{1443}$, e.g., the half value of Radium "B" = $\frac{38.7 \times 1000}{1443} = 26.8$ minutes approx.

It is believed that 1 atom of a radioactive body expels α particle only at each disintegration.

INTERNATIONAL TABLE OF THE RADIOACTIVE ELEMENTS AND THEIR CONSTANTS (1926)

$\lambda \text{ (sec)}^{-1}$ is the *radioactive constant* of the *equations of transformation*:

$$dQ = -\lambda Q dt, \quad Q = Q_0 e^{-\lambda t} \quad \log_e \frac{Q}{Q_0} = -0.4343 \lambda t.$$

in which Q_0 is the initial quantity and Q the quantity remaining after a time t (seconds).

$\lambda = -\frac{dQ}{Q} \cdot \frac{1}{dt}$ represents the fraction of the element transformed, reduced to the unit of time.

In the case of a double transformation, the values between brackets [] refer to the constants corresponding with the separate branches; the constant for both branches not being put between brackets.

The sign (?) indicates that the value has been indirectly deduced from the range of the α rays expelled.

$$\theta = \frac{1}{\lambda} \quad \text{is the average life of the radioactive atoms.}$$

T is the *half period*, i.e. the time in which the quantity of radioelement is diminished to one half:

$$\lambda T = -\log_e 0.5 = 0.69315 \quad \text{and} \quad \theta = 1.443 T$$

Radiation. The brackets () indicate that the radiation is relatively feeble. α_0 is the *range* in cm. of the α rays in air at 0° C. and a pressure of 760 mm. of mercury.

The range at $\tau^\circ \text{ C.}$ and under p mm. of mercury is

$$\alpha = \frac{\alpha_0 (273 + \tau) 760}{273 p}$$

V is the velocity of α or β rays relatively to that of light.

To convert to cm. per sec. multiply by 3×10^{10} .

For the α rays:

$$V = 0.0342 \alpha^{\frac{1}{2}}$$

β_{Al} is the *absorption coefficient* of the β rays in aluminium, the thickness being measured in cm.

$\mu_{\gamma Al}$ and $\mu_{\gamma Pb}$ are the absorption coefficients of the γ rays in aluminium and lead respectively, the thickness being measured in cm.; the latter is given for the most penetrating type of γ rays.

If I_0 is the initial intensity and I the intensity after the rays have traversed x cm. of the absorbent:

$$I = I_0 e^{-\mu x} \quad \log_{10} \frac{I_0}{I} = 0.4343 \mu x$$

If D is the thickness corresponding with the absorption of one half of the rays:

$$\mu D = 0.693$$

REMARKS CONCERNING THE NOMENCLATURE IN THE INTERNATIONAL TABLE

It is desirable that the nomenclature adopted by the International Commission should be accepted universally but that put forward is provisional, to serve as a basis of discussion with the view to the adoption ultimately of a standard nomenclature.

The most important points are:

1° The three radioactive emanations have been given the names radon, actinon, and thoron, with the symbols Rn, An, Tn, to suggest both their origin and their chemical character as members of the family of the rare gases of which the valency is zero;

2° In the branches which occur at the C members the sign (') has been used to indicate the products resulting from the emission of β rays (isotopes of polonium) and the sign (") to indicate the products resulting from the emission of α rays (isotopes of thallium);

3° The ultimate products have been indicated by the letter Ω .

EXPLANATION OF THE NOTES

Note 1. *Uranium I.* The value given for θ is that obtained from the equation:

$$\theta = \frac{1}{\lambda} = 2440 \times 0.97 \times 3 \times 10^6 \times \frac{226}{238} = 6.75 \times 10^9$$

in which the number 2440 represents the average life of radium in years, the number 0.97 the branching coefficient and $3 \times 10^6 \times \frac{226}{238}$ is the ratio between

the numbers of atoms of uranium and radium in equilibrium in minerals.

If the actinium series is independent from that of uranium I, λ cannot be calculated by this method.

The value of λ obtained by the direct counting of the α particles from a compound of uranium is 4.57×10^{-18} from which $\theta = 7 \times 10^9$ years and $\lambda = 4.8 \times 10^9$ years.

Note 2. *Uranium X₂* is also called brevium.

Note 3. *Radon* replaces the names *radium emanation* and *niton* (the latter of which was proposed by Sir William Ramsay).

Note 4. *Radium C* undergoes a double disintegration: 99.97% of the atoms emit β rays and produce the substance RaC' which gives α rays, and 0.03% of the atoms emit α rays and produce the substance RaC'' which gives β rays.

Note 5. *Radium D* is also called radiolead.

Note 6. *Radium C''* is also called radium C₂.

Note 7. *Uranium Y* is the first known member of the actinium series. It may be derived from uranium I or uranium II. In this case, 3% of the atoms of uranium produce the actinium family, and 97% the radium family.

The hypothesis has also been put forward that the actinium series may be produced independently from a third (hypothetical) isotope of uranium for which the name actinouranium has been proposed.

Note 8. *Protoactinium* is also called ekatantalum.

Note 9. A new radioactive substance named *uranium Z*, and isotopic with protoactinium, accompanies uranium in minute quantity. (*Berichte*: 921, 54(B), 1,131). Its period is from 6 to 7 hours. It emits a β radiation for which DAI varies from : 0.0014 to 0.012. Its parent is an isotope of thorium, but it cannot yet be placed in the series.

Note 10. *Actinon* is also called the actinium emanation.

Note 11. *Actinium C.* 0.2% of the α rays emitted by this substance have range $\alpha_0 = 6.10$, instead of 5.12. From this it has been concluded that 0.2% of the atoms undergo a transformation by the emission of β rays as is the case in the radium C and thorium C branches (*Phil. Mag.*, 1914, (VI), 27, 690; 3, 818). Confirmatory evidence appears to be desirable.

Note 12. *Actinium C''* is also called actinium D.

Isotope	Radiation	α_o	V	$\mu\beta Al$	$\mu\gamma Al$	$\mu\gamma Pb$	Notes
U Th Pa U Th	α β $\beta (\gamma)$ α α	2·37 2·75 2·85	0·0456 0·0479 0·0485	1 2
Ra.	$\alpha (\beta + \gamma)$	3·13	{ α 0·0500; β 0·52; 0·65 }	312	354; 16; 0·27
Rn Po	α α	3·94 4·50	0·0540 0·0565	3
Pb	$\beta (\gamma)${	0·36; 0·41; 0·63; 0·70; 0·74	} 13·1; 80	230; 40; 0·51
Bi	{ 99·97% } β and γ	{ 0·786; 0·862; 0·949; 0·957 }	13·2; 53	0·115	0·50	4
Po Pb Bi Po	α (β and α) β $\alpha (\gamma)$	6·57 3·58	0·0641 0·33; 0·39 0·0523 5500 43·3 45; 0·99 585 5
Pb
Bi Tl Pb	0·03% α β	? 6

ACTINIUM

U	α	7
Th	β	About 300	8, 9
Pa	α	3·314	0·0510
Ac	—
Th	$\alpha (\beta)$	4·36 {	α 0·0559; β 0·38; 0·43; 0·49; 0·53; 0·60; 0·67; 0·73 }	About 170	25; 0·19
Ra	α	4·17	0·0550
Rn	α	5·40	0·0600	10
Po	α	6·16	0·0627
Pb	(β and γ)	Very large	120; 31; 0·45	11
Bi	α	5·12	0·0589
Tl	β and γ	28·5	0·198 } to 1·8 }	12
Pb

Disintegration of Radium. Lead is viewed as the end product (pitchblende invariably contains lead), and with each change there is an outburst of energy (*cf.* also p. 691).

Ionium is an intermediate product between uranium and radium. Ionium present in commercial uranium salts is identical chemically with thorium and cannot be separated from it. F. Soddy, *Pharm. J.*, i/1912, 394. *See also* the Thorium Disintegration Products.

Relation between the Uranium and Actinium Series.—Research on the γ rays of radium throw fresh light on the peculiarities seen in the absorption of these radiations and on their wave-length.

A great deal of research on the absorption of γ rays has been carried out, and has thrown light both on the structure of the outer atom and also on the structure of the nucleus. Under the action of the rays, high speed electrons are emitted and also in some cases neutrons.—*See* Rutherford, Chadwick and Ellis, *Radioatoms from Radioactive Substances*.

Ekatantalum (*Syn.* PROTOACTINIUM). *The Parent of Actinium.*

According to Prof. Soddy, "it was expected that uranium-Y isotopic with uranium-X, and ionium in the thorium place in the periodic table, and simultaneously formed with one of them in the dual α ray change of either uranium I or uranium II, would prove to be the first member of the actinium series. Uranium-Y gives a β -radiation, and therefore its unknown product must occupy the ekatantalum place in the periodic table and be *isotopic* with uranium- X_2 or brevium, the very short-lived product of uranium-X, in β ray change."

There is no reason to doubt that ekatantalum is the product of uranium-Y, but this probably, as in the production of uranium II from uranium- X_2 , can never be the subject of direct proof owing to the unfavourable relations of the periods. There remains the doubt, however, as to whether uranium-Y is the product of uranium I or uranium II, although the latter is perhaps the more probable.

With exceptions the complicated disintegration sequences of the radioactive elements are now unravelled and are indicated in figures reproduced in the *Ann. Rep. Chem. Soc.*, 1919 (Vol. XV), p. 200.

The raw material for the preparation of protoactinium is the insoluble residue, consisting chiefly of silica, from pitchblende after treatment of the mineral with nitric acid. It is recommended to add $\frac{1}{2}\%$ to 1% of tantalum oxide to the residue and to heat with a little concentrated sulphuric acid and an excess of 40% hydrofluoric acid in a platinum vessel, properly cooled, then to dilute and filter through a paraffined funnel, evaporate the filtrate, and ignite gently. This renders the tantalum oxide containing the protoactinium insoluble in acids. Efforts to concentrate it from tantalum have recently succeeded.

Chemical Identity of Radio-Elements. Uranium-X and radio-actinium are chemically identical with thorium; mesothorium-2 is chemically identical with actinium; radium-A is chemically identical with polonium; radium-C, thorium-C, actinium-C, and radium-E are chemically identical with bismuth; radium-B, thorium-B, and actinium-B are chemically identical with lead; thorium-D and actinium-D are chemically identical with thallium.—A. Fleck, B. Assocn., 1913.

For an account of isotopes see p. 669.

Polonium.—This is another radioactive element discovered by Mme. Curie in pitchblende, which gives off the α rays almost exclusively. Using a preparation of polonium small enough it is possible to reduce the impacts of the α particles to 1 or 2 per second.

By aid of a loud-speaking telephone, it is possible to hear polonium breaking into α particles (helium).

Polonium is identical with radium-F. It has a half value of 136.3 days. Polonium and radium are present in a ratio of 1 : 5000.

The quantity of polonium in a radium mineral is 1 mg. of polonium for every 4 tons of uranium.

Since polonium is the last of the active products in the radium series it is to be expected that it should be transformed into helium and lead, one atom of helium and one atom of lead from each atom of polonium—this point of view is further substantiated by the fact that before the formation of radium-F seven α particles are successively given off, each of which being an atom of helium has the atomic weight 4. Therefore the atomic weight of polonium would appear to be $(4 \times 7 =) 28$ less than that of uranium, i.e., $238.5 - 28 = 210$ —this loses an α particle, i.e., 4, giving a final atomic weight of 206.5—a value very close to that of lead.—Rutherford.

The rays from radioactive substances are of (at least) three main types :—

(1) The α rays, non-penetrating and only slightly deviable in a strong magnetic field, deviation about $\frac{1}{160}$ part of that of the β particle—the direction being opposite to that of the β . (2) The β rays, moderately penetrating, deviable. (3) The γ rays, exceedingly penetrating, non-deviable.

When speaking of β and γ radium rays, what are really intended are the β and γ rays of Radium C and C'. The emanation like radium itself gives only α rays.—(*vide* table above.) The whole of the β rays result in the later changes of the active deposit.

The α rays. These are demonstrated by Crookes' Spinthariscopes.

99% of the total energy of radium is due to the α rays, the β and γ being responsible for the remainder.

The α rays from radium are complex—4 different types, each with a definite "range" or distance it will travel in any absorbing medium. The most penetrating type according to Bragg travels in air at atmospheric pressure and ordinary temperature 71 mm. (just under 3 inches) and no more. This fact is made use of in a most convincing lecture experiment in which bare radium bromide is placed in the centre of a flask coated inside with Sidot's Blende (crystalline zinc sulphide), there is no marked effect until the air is rarified by means of a pump—at the first stroke of which the Blende begins to glow.—F. Soddy.

The ranges of α rays in air vary from 8.62 cm. for thorium C' to 2.73 cm. for uranium.

The fastest α particle is completely absorbed by the time it has travelled 2 inches in air. As a general rule this particle travels further in light gases, e.g., hydrogen, than in heavy, e.g., carbon dioxide.

The α rays are absorbed also by glass, mica, a thin sheet of aluminium, or indeed a sheet of note paper. Glass, however, can be blown so thin as to allow the radiation to pass through.

The rays constitute electrically charged atoms travelling at various speeds, each α particle being associated with 2 unit charges of + electricity. Crystalline zinc sulphide is very markedly

sensitive to them though much less to the β . Barium platinocyanide and willemite, on the contrary, are more affected by the β than the α rays. The mass of the α particle is about four times that of the hydrogen atom, and is enormous in comparison with that of the particles composing the β rays. The α particle is a helium atom (*v. Helium*). This accounts for the feeble penetrative power of the former.

The "law of density" governs the penetration. The total distance traversed is known as the "range" R . The velocity of the particle is given by the relationship:

$V^3 = aR$, where V is the velocity and a a universal constant.

The question as to mass, or volume, of the preparation comes into consideration in the case of the α rays,—the more the surface is spread out the less absorption there is of α radiation by the substance itself. The α rays from 1 mg. of radium produce more electrical effect than the β and γ rays from 30 mg., e.g., in discharging a silk tassel.

Rutherford has shown that at the point where the α particle is no longer detectable it is still travelling at 5000 miles a second. Beyond this, fluorescent and electrical actions all cease simultaneously. It follows that since α particles expelled at a velocity below 5000 miles per second cannot be detected, doubtless there are such changes akin to radioactivity which may be proceeding without our knowledge.

All substances absorb α rays proportionally to the square root of their atomic weights, if elementary, or to the sum of the square roots of the weights of the constituent atoms, if a compound or mixture.

All α particles have the same mass and differ only in the initial velocity of expulsion whether expelled from radium emanation, uranium, thorium, or any other bodies which expel them.

Rutherford succeeded in detecting helium outside a sealed thin glass vessel containing radium *in vacuo*—the glass being thin enough to allow the α particle to pass—this being a further point towards proof that the α particle is an atom of helium. He has also counted the number of α particles expelled from a given quantity of radium every second. A milligram emits 370 million per second.

The α particle carries two atomic charges of positive electricity, i.e., it is a divalent ion.

The speed of α particles is such that the life of each α particle is completed in about $1/1,000,000,000$ second.—Sir W. H. Bragg.

A photographic plate contained in a special form of dark slide may be used in place of willemite screens to demonstrate positive rays, thus giving permanent records.—Sir J. J. Thomson.

The α particles expelled in any one type of disintegration travel with exactly the same velocity—which is gradually diminished to exactly the same extent for each particle in passage through a homogeneous absorbing medium. The ionisation produced in any given length of its path *increases* as the velocity of the particles diminishes to the critical velocity, when all effects cease abruptly and the α particle is absorbed or passes beyond means of detection. The *range of the α particle* is, therefore, an important constant.—F. Soddy.

In **luminous paints** composed of radium and zinc sulphide the zinc sulphide undergoes rapid deterioration—the rate of decay in luminosity is proportional to the amount of radium present, but not exactly proportional. Radium paint made according to **Admiralty specification** containing 0.4 mg. of radium bromide or its equivalent (in 1 g. of zinc sulphide) has a luminosity of about 0.03 foot candles, while a paint containing half this amount of radium has more than half the luminosity. The sample containing 0.4 mg. will die at a much more rapid rate than the other—the weaker preparation has a *much longer life*. This is not generally known. In the manufacture of radium paint the α particle is by far the most effective to use for bombarding zinc sulphide.

The α particle from thorium C' has a longer range, 8.62 cm., than that of radium (6.97 cm.)—the α particle will travel through this distance in air in not exceeding 1/1000,000,000 second. The particle in question from thorium C' is therefore more effective in producing luminosity, but against this is the disadvantage of the relatively short life as compared with radium. If mesothorium had a life equal to that of radium, the half period of which is 2,000 years against 5.5 for mesothorium, it would be advantageous to use it. Old samples of radium are better than others for making paints, the explanation being that old radium is richer in the disintegration product "F"—in fact the α radiation of radium increases for the first 100 years. Ionium would be an ideal excitant—the radiation from this consists of α particles only and its half period is even longer than that of radium.

In making radium paint the best method is to place a little of the mixed powder in a watch glass in a heap, moisten it with turpentine and then add about an equal amount of mastiche varnish and apply with a sable brush, taking care that the crystals of zinc sulphide are not broken. **Spodumene**, a native form of lithium, exposed to radium rays, is luminescent on warming. **Balmain's paint** (calcium sulphide) is improved by the presence of traces of bismuth.

For an account of manufacture of luminous paints, see Pharm. J., ii/1921, 185.

Chemical action of α -rays on hydrogen sulphide, ammonia, nitrous oxide and CO_2 . The last is only very slowly decomposed.—*J. chem. Soc. Abstr.*, ii/1920, 214.

The β Rays. β rays are deviable in an electric field. They consist of negatively charged electrons much lighter than the α particles, and have a mass about 1/1850 that of the hydrogen atom. Their speeds reach 0.99 of the velocity of light.

The β rays are 100 times more penetrating than the α rays, being reduced to half value by passage through 0.05 cm. of aluminium. They are, however, *absorbed for the most part by 1 mm. of lead*.

3 or 4 mm. of aluminium or 1 inch of cardboard is sufficient to absorb all β rays, while γ rays have been shown to pass through 20 cm. of lead or 2 feet of iron.—Rutherford.

The velocity of the particles of the cathode rays in a discharge tube is variable with the potential applied to the tube, the speed being proportional to the square root of the voltage. That of the fastest of the β particles of radium is as high as 170,000 miles per second, i.e., approaching that of light, but in addition there are various types of "soft," feebly penetrating, slowly travelling β rays. Cathode rays, i.e. high speed electrons, have been shown also to behave like waves in showing diffraction effects. Their "wave length" is inversely proportional to their speed.

The α and β rays "ionise" the gas through which they pass, making it capable of conducting electricity. The Hon. R. J. Strutt devised a **Radium Electroscope** for showing the dissipation of the negatively charged rays. This apparatus was fully described in earlier Editions.

The γ rays which usually accompany the β rays, are analogous to X-rays produced by cathode rays.

γ rays are identical with X-rays except that they are as a rule far more penetrating. They are given off by a number of elements and are about 100 times more penetrating than the β , being reduced to half value by 6 to 7 cm. of glass or aluminium.

The γ rays from radium are cut down to half the intensity by about 7 mm. of lead. The final linear absorption coefficient in lead is approximately 0.50. According to Rutherford they can be detected after passing through 20 cm. of lead.

They are about 10,000 times more penetrating than the α rays. When γ rays pass through matter, β radiation is emitted, moving chiefly in the direction of the original γ but afterwards scattering in the ordinary manner of β rays; γ ray quanta also strike electrons setting them in motion, and the "recoil electrons" thus produced are of great importance in the therapeutic use of radium. The penetration and therefore speed of the β radiation thus produced increases with the penetration of the γ radiation to which it is due.

Heat Evolution. Half a grain of radium bromide evolves, according to F. Soddy, about 2 calories of heat every hour—in 4 years 70,000 calories. Half a grain of coal gives out during complete combustion only about 250 calories; that in the period in question (4 years) radium emits nearly 300 times the energy obtainable from the same weight of coal. 98% of the heating effect of radium is due to the α particles.

It is unwise to keep radium in solution in a sealed vessel as the gradual production of hydrogen and oxygen may cause it to burst. Carbon dioxide, ammonium and hydrochloric acid are also decomposed by it.

Radon (Radium Emanation). *Syn.* Niton

Radium gives off a gaseous emanation allied to the argon family. It may be regarded as radium that has lost an α particle. It should occupy one of the two vacant places in this group in the periodic table. It is inert—not capable of absorption by chemical means. Radon disintegrates in definite stages, and in doing so gives out the various rays—see Table on pages 682 and 683. It is devoid of chemical activity, and follows Boyle's law. Its boiling point at standard pressure was found by Rutherford to be -65° . Gray and Ramsay considered the emanation cannot exist as a liquid below -71° .

The gas is given off without appreciable loss of weight of the original matter, and can be aspirated through a tube and be made to condense at -150° by freezing with liquid air.

Itself strongly luminous, it causes willemite to glow brilliantly in the dark. It can be filtered through wool. It was found by Sir W. Ramsay and Prof. Soddy to give the helium spectrum on keeping 3 or 4 days; in fact, the emanation produces helium by its α ray activity.

Ramsay found that in 3.7 days the amount of luminous gas was only half its original size, and in thirty days it was only the smallest pin-point in the tube.

This reduction in volume is concurrent with the change from the gaseous to the solid state (*v.* Table above). When a radium

salt is dissolved in water and the liquid evaporated to dryness, the radium will be found to have lost the greater part of its radioactivity, i.e., the intensely radioactive emanation will have passed off, on dissolving, in the form of a gas, unless steps are taken to prevent its disappearance. The β and γ rays will have disappeared, and the α rays will be only a quarter as powerful as initially—the activity, however, gradually recovers in a month.

The emanation decomposes water, hydrogen being 3% in excess, and will cause the gases to recombine.

The volume of helium produced from 100 volumes of emanation is about $3\frac{1}{2}$ volumes, agreeing with the view that the α particle is a helium atom.

An atom of helium and an atom of emanation are simultaneously produced when an atom of radium is disintegrated, but when the quantity of emanation has reached its maximum it does not accumulate further with further lapse of time. The emanation is absorbed by cocoanut charcoal at ordinary temperature and pressure. On heating the charcoal the emanation is driven off, and can thus be concentrated. This process has been used for extracting the emanation always present in the atmosphere.

Standards for Radium Emanation. The unit of emanation is called the “**Curie**” and is the quantity of emanation in equilibrium with 1 g. of radium element. Smaller amounts are stated in terms of the “**Millicurie**” and “**Microcurie**”—the millicurie being the emanation in equilibrium with 1 mg. and the microcurie with 1/1000 mg.

Other arbitrary standards not now officially recognised are the **Gram-second** and **Milligram-minute**. The former is the amount of emanation freed from 1 g. of radium element during 1 second.

The **Mache Unit** used for measuring the small amount of electricity in certain radioactive waters depends on the saturation current leak through an electroscope, due to the emanation and its products radium A and radium C. *It is the quantity of radium activity which causes a leak of 1/1000 of an electrostatic unit of current under certain conditions.*

The Mache Unit is a minute one whereas the Curie is a large one. The emanation combined in 10 litres of mineral water moderately radioactive is of the order 0.1 microcurie.

The units compare as follows:—

Curie	Millicurie	Microcurie	Milligram-minute	Mache
1	1000	1,000,000	7,992,000	2,500,000,000
0.000001	0.001	1	7.992	2,500

1 “Electrostatic Unit” = 1000 Mache Units.—*cf Brit. med. J.*, i/1913, 118; i/1913, 1107.

A slide rule for radon dosage calculations.—W. V. Mayneford, *Brit. J. Radiol.*, Dec., 1928.

Radioactive Deposits. Solid substances in the immediate neighbourhood of a radium salt acquire “**Induced Activity**.” After removal, the activity decays abnormally rapidly at first, but subsequently in geometrical progression; $\frac{1}{2}$ value 30 minutes. “Induced activity” consists of emission of α , β and γ rays. It is in the form of an “active deposit.” In this active deposit changes take place several times in quick succession. The bodies are termed radium A, radium B, radium C, radium C₂, and radium D.

In the case of thorium the “induced activity” lasts a few days, whilst that of actinium decays slightly more slowly than that from radium.

Secondary β radiation may be well shown by placing a tube of radium above a photographic plate face downwards on a piece of metal, e.g., platinum, covered by a piece of black paper; there results darkening of the plate. The photographic

efficiency of this secondary radiation is greater than that of the primary radiation which has already passed once through the film.

The hardness or penetrability of secondary rays produced by impact of radium rays is governed by the atomic weight of metal giving rise to them.

Substances such as lead foil or common salt placed in the neighbourhood of radium become coated and can be similarly used for superficial applications. Sodium chloride so treated is sometimes dissolved in water and used for injection purposes.—W. E. Dixon, *Brit. med. J.*, i/1929, 239.

Very recently it has been discovered that many substances may be made radioactive artificially by bombardment with neutrons, i.e., particles having high speeds and a mass nearly that of a proton but no net electrical charge. Such neutrons may be produced by α rays or γ rays on beryllium. This induced radioactivity is in general very feeble but is a real **artificial production of radioactive materials** and must not be confused with the "induced activity" above. We now have definite evidence of the production of artificial radioactivity.

Early in 1934 M. and Mme. Curie-Joliot demonstrated the possibility of manufacturing radioactive substances. They found that when boron or other substances were bombarded with the swift alpha particles, or nuclei, of helium atoms, emitted from the naturally radioactive substance polonium, they emitted positive electrons, and the emission of these electrons continued after the polonium source of bombarding particles had been removed. The radioactive atoms produced in the boron consist of a form of nitrogen which they named "**radio-nitrogen.**" Cockcroft and Walton later demonstrated that radio-nitrogen could be manufactured in their chemical apparatus by bombarding carbon with protons, or nuclei, of hydrogen atoms. It is important to realise that this artificial radioactivity is rather different from the natural radioactivity: radio-nitrogen emits positive electrons when it disintegrates—natural radioactive substances emit wave radiations, the nuclei of helium atoms, and negative electrons.—*Brit. med. J.*, ii/1934, 689.

Helium is occluded in various minerals especially those of uranium and thorium. This suggested to Ramsay and Soddy the investigation which led to the proof that radium emanation is in part helium.

In some instances its volume is nearly 100 times as great as the volume of the mineral from which it was obtained.

Helium has been liquefied at -270° , i.e., only 3° from absolute zero.

Helium is one of the ultimate products developed from radium, uranium and thorium, formed slowly but, nevertheless, fast enough to ensure that all minerals containing these elements must contain helium also. The α particle from radium is an atom of helium. There is produced simultaneously an atom of radon.

Taking the atomic weight of helium as 4, this inert gas fits in with other members of a like nature, viz., *neon* at. wt. 20, *argon* 40, *krypton* 83, *xenon* 130.

50 mg. radium, it has been stated, produce 0.000018 mg. helium in 60 days, or 0.0022 mg. in 1 year from 1 g. of radium bromide. About 2 mg. of helium are produced from 1000 tons of uranium per annum. It is possible to draw conclusions as to the age of geological formations from the accumulation of helium in them.

F. Soddy detected the production of helium from uranium and thorium—the amount is $1/500,000,000,000$ of the uranium or thorium per annum, which accords with theory. The method of detection depends on the use of strongly heated calcium metal which, *in vacuo*, absorbs all gases except helium.

An analysis of the atmosphere shows that one cubic metre contains

Argon	9.323 litres.
Neon	18.1 ml.
Helium	5.4 ml.
Krypton	0.049 ml.
Xenon	0.0059 ml.

Prof. Moureu has definitely established that the rare gases are present in the external atmosphere surrounding the earth, and also in the air found in the interior of the earth.—*Chem. & Drugg.*, i/1923, 869.

Commercial Use of Helium. Helium is present in gases, minerals, springs—at some springs in France as much as 5% is present. Prior to 1918 the total amount isolated did not exceed three or four cubic metres. It is twice as heavy as hydrogen (the atmosphere being 14.4). Next to hydrogen it is the lightest gas known. It enters into no combinations, and is quite inert: it is non-explosive. It was suggested in 1914 instead of hydrogen to fill the envelopes of airships. Its rate of diffusion through the envelope is 30% less than that of hydrogen. At Bow Island a supply of 10,500,000 cubic feet is available annually. It is conveyed by pipes to Calgary where first nitrogen with a content of 5% helium is obtained, while liquid methane, pentane and butane are also produced in large amount. By submitting this 5% helium to a temperature of -163° at a pressure of 25 to 30 atmospheres helium of 87% to 90% purity is isolated, and this can be further purified by means of liquid air. Hydrogen with a content of 20% helium is still non-inflammable.—Prof. J. C. McLennan, *J. chem. Soc.*, 1920, 923; *Chem. & Drugg.*, 1920, 845; *Lancet*, i/1920, 164; *Nature, Lond.*, i/1920, 360; *ibid.*, ii/1920, 747.

30,000 to 40,000 cubic feet are extracted daily from natural gas in the U.S.A. It is compressed in steel cylinders and stored, and its export is prohibited. It possesses 92% of the lifting power of hydrogen. Mercury at the temperature of liquid helium (490°F . below the freezing point of water) has a remarkable super-conductivity. No natural gas within the Empire has been found to contain as much as $\frac{1}{2}\%$ of helium, whereas in Texas gases containing 1% to 2% are available.—Prof. J. C. McLennan, *J. Röntgen Soc.*, Oct., 1924, 171.

Artificial Transmutation. The transmutation of one element into another is an accomplished fact. The first experiments by Rutherford in 1919 on bombarding nitrogen with α particles showed that nitrogen could break up, giving high speed hydrogen atoms. This was extended in 1922 to a number of light elements, e.g., boron, sodium, aluminium. Recently it has been shown that under the bombardment of high speed particles, produced in a discharge tube run at, say, 600,000 volts, many light elements may be broken up and new atoms produced. The artificial production of radioactivity by neutrons is also accomplished by the absorption of the particle by the parent atom, the rearranging of the particles to form new, often unstable, atoms. These subsequently break up emitting other radioactive particles. The amounts of new elements produced are extremely small and the process extremely inefficient.

If uranium is bombarded with neutrons its atoms appear to be transmuted into atoms of an entirely new type. Fermi suggests that the new element has an atomic number of ninety-three.—*Brit. med. J.*, ii/1934, 689.

Radioactivity may be regarded as one phase of the cycle of evolution of matter; the other phase, the construction, is infinitely slower. The radioactive phase is virtually the culmination of the long constructive phase during which atomic complexity has increased to such an extent that it eventually leads to instability. The present elements are the remains doubtless of the materials of long years ago.

Atomic energy. If hydrogen could be transmuted into helium, energy could be produced in quantities prodigious beyond the dreams of scientific fiction.

For 1 gramme-atom of hydrogen, i.e., the amount contained in 9 ml. of water the energy expressed in terms of heat is 1.6×10^{11} calories, or, in terms of hours 200,000 kilowatt-hours. There is enough power in a tumbler of water to drive the *Mauretania* across the Atlantic and back at full speed.—F. W. Aston *Brit. J. Radiol.*, 1926, 12.

Radium in the atmosphere is present to the extent of 60×10^{-12} g. per cubic metre. The air in the upper atmosphere (10 to 50 miles up) has been shown to be considerably ionised, possibly due to the direct radiation from the sun largely by ultra-violet light and high speed particles, or, for instance, cosmic rays.

Action on Bacteria, Toxins, Ferments, Blood, etc. The fact seems to be clear that radium rays are not bactericidal to any extent. L. Barlow, however, detected a bactericidal action and predicted the use of radium in bacterial diseases as well as in malignant growths.

In a series of experiments upon diphtheria toxins, quantities of radium sulphate varying from 20 to 50 micrograms were placed in contact with the toxin for 30 days—with non-radiferous toxins the "control" guinea-pigs died within from 24 to 72 hours after inoculation, but the animals inoculated with the radiferous substance survived for at least 5 to 12 days, and in some cases for 20 to 30 days. A similar difference between the action of the radiferous and non-radiferous toxin was discovered using emulsions of the living Koch bacillus. Radium has no retarding influence, however, on the virulence of tetanic toxin.—*Brit. med. J.*, ii/1911, 1025.

Radiation is stated rapidly to destroy the ferments emulsin, pepsin, trypsin and ptyalin.

Blood *in vitro* mixed with radium emanation. Hæmolysis occurs, with gradual conversion of oxyhæmoglobin into methæmoglobin. The hæmolysis is due to α radiation. Leucocytes show marked degenerative changes when exposed to α rays. The specific properties of opsonin and hæmolytic complement are lost when serum is exposed to α rays. The progressive changes caused by these rays indicate the separate identity of opsonin and complement. The β and γ rays yielded negative results in analogous experiments.—H. Chambers and S. Russ Roy. Soc., June, 1911, per *Nature*, i/1911, 540.

Radioactive bodies are probably poisonous, acting directly on the nerve centres. If radium emanation were used criminally the excited activity would have to be sought for, and probably would not be found, whereas if an actual radium salt had been administered even the ashes of the dead body would show the necessary radioactivity to convict the murderer.

α , β and γ rays of radium arrest acetous fermentation in dose of 1 microgram per cent. of liquid; a smaller dose accelerates fermentation.—Laborde *J. Pharm. Chim.*, 1922, 26, 44; *Yearb. Pharm.*, 1923, 147.

Radium Emanation Water. Dose: Half a pint a day six days a week for six weeks for patients suffering from rheumatic gout and similar affections was advised by the late Sir F. Treves. Two such courses generally effect a cure. This refers to the Radium Institute product which is stated to be 4000 to 5000 times stronger than spa waters.

It must be emphasised that the ingestion of quantities of radium or radioactive salts is highly dangerous. If radioactive water contains only radon, this material will practically have lost its activity in a month, but if the radioactive water contains radium itself, the activity is permanent and may lead, in sufficient quantities, to very serious results.

The danger of commercial radioactive preparations (drinking waters, pills, etc.) is not so much that they do not contain what they claim to, but that they contain a deadly poison. It has been shown that 10 micrograms (0.01 mg.) of radium distributed over the whole skeleton is sufficient to produce a horrible death years after ingestion. In the case of one American preparation containing mesothorium and radium the directions called for the use of amounts of radioactive substances to be swallowed equal to those taken by luminous dial painters whose deaths were directly attributable to radium poisoning.—A. H. Colwell and Sidney Russ, *Lancet*, ii/1932, 223.

Sea Water in the North Atlantic contains about 0.9×10^{-12} g. radium per litre, i.e., 1 billionth part of a gramme per litre, various other sources yielded an average of 16×10^{-12} g. per litre—the amount in river waters is less, e.g. about 1/4 that of Atlantic water for the St. Lawrence and the Nile. The amount in the water of the Atlantic is said to be about 1/20 that in a weak radioactive spring.—S. Russ.

The sea contains about 20,000 tons of radium. One ton of radium is equal to 1,500,000 tons of coal in energy. One gramme of radium gives off in its lifetime about 3,000 horse power.—C. E. S. Philips, Cancer Hospital Lecture, 10/12/1913.

All materials contain minute quantities of radioactive material of the order of 10^{-13} g. per millilitre.

Pitchblende Ointment. Pitchblende 25%, finely powdered, in soft paraffin. Employed in the palliative treatment of malignant growths.

Radium Ointment, Radium Salve. Preparations under these names have been supplied commercially.

Radio-active Mud.—Continental spas with a reputation for treatment of rheumatic affections by mud baths probably owe their results to the fact that the mud is radioactive. Such mud can only be used at the source.

Uranium Mud or Actiniferous Earth is similar; it is understood to be the by-product formed during the process of the breaking up of uranium ores. Its radio-activity is said to be due to traces of radium, polonium, and, in particular, of actinium. It emits emanation of low activity.

Rheumatic arthritis, gonococcal rheumatism, nerve affections and skin diseases have been treated by compresses and pads of the mud, or by the use of the mud in baths, about 8 oz. to 40 gallons of warm water. The length of application of pads varies with the case.

Radioactive mud from wells in Pistany, Czecho-Slovakia, for making into poultices.—*Lancet*, ii/1922, 744.

The therapeutic action of mud baths.—E. Duhot, *Paris méd.*, Apl. 18, 1925, 345, *per Prescriber*, 1926, 134.

Thorium and its Disintegration Products.

Thorium and Mesothorium are obtained from **monazite sand**. Travancore, in the extreme South of India, is a source of origin, as is also Brazil. The sand contains 5% to 7% ThO_2 , 25% to 30% Pb_2O_5 , 25% to 35% Ce_2O_3 and 20% to 30% La_2O_3 , Pr_2O_3 and NdO_3 . Titanium white, a titanite of iron, is obtained in working. It is used as a paint for interiors—it is innocuous and does not blacken in town air. The yield of mesothorium from the raw material is 6 to 7 mg. per ton.

Thorium changes, broadly speaking, into mesothorium, and this to radiothorium, and this to thorium X, and this to a series of other products. The following are the disintegration data as to thorium (*cf.* radium chapter).

Thorium shows an activity, measured by α rays, about the same as pure uranium compounds, but the β and γ ray activity is feebler. In the by-products of a single year's manufacture of thorium for the mantle industry the mesothorium and radiothorium capable of being extracted possess, it has been stated, as much radioactivity as at least an ounce of pure radium.

Thorium X is prepared from pure thorium salts (which always contain radiothorium, the immediate parent, in considerable amount). It is obtained by addition of ammonia to a solution of a thorium salt, evaporation of the filtrate and removal by ignition of the ammonium salts. It is transformed directly into emanation so that the rate of production of emanation is directly proportional to the amount of thorium X. About a month after removal of thorium X the thorium regains its original activity, and shows an α ray activity equal to about one-quarter of its value before separation. This was at first thought to be the activity due to thorium itself, but later work has shown that this residual activity is due in part to unseparated products. After separating the

thorium from the Ceylon mineral thorianite, which yields large quantities of helium, Hahn found a radioactive substance of slow rate of transformation in the residues which gave rise to thorium X, and the thorium emanation—radiothorium.

Radiothorium is not separable from thorium by any chemical processes. Hahn found that other radioactive products must be present in thorium. On examining commercial preparations of thorium of known ages, it was found that the α ray activity of thorium after separation decreased at first for some years, passed through a minimum, and then slowly increased again to a final value represented by the activity of a pure thorium compound from which none of the radioactive constituents had been separated. To explain this it was necessary to assume the existence of another product in thorium called **mesothorium** which had been produced from thorium and was transformed into radiothorium.

THORIUM
from the International Table

T	$\theta = \frac{1}{\lambda}$	$\lambda \text{ (sec.)}^{-1}$	Name	Symbol	Atomic	
					Wt.	No.
1.31×10^{10} yrs 6.7 yrs	1.89×10^{10} yrs 9.67 yrs	1.68×10^{-18} 3.28×10^{-9}	Thorium Mesothorium 1	Th MsTh1	232 228	90 88
6.2 hours	8.9 hours	3.12×10^{-5}	Mesothorium 2	MsTh2	228	89
2.02 yrs	2.91 yrs	1.09×10^{-8}	Radiothorium	RdTh	228	90
3.64 days 54 secs 0.14 sec 10.6 hours	5.25 days 78 secs 0.20 sec 15.3 hours	2.20×10^{-6} 0.0128 5.0 1.82×10^{-5}	Thorium X Thoron Thorium A Thorium B	ThX Tn ThA ThB	224 220 216 212	88 86 84 82
60 mins	87 mins	1.92×10^{-4} [1.25×10^{-4}]	Thorium C—	ThC	212	83
10^{-11} sec	10^{-11} sec	10^{11} (?)	Thorium C' Thorium Ω'	Th C' Th Ω'	212 208	84 82
.....	(Lead)	Pb ²⁰⁸
.....	(6.7×10^{-5})	Thorium C—	ThC	212	83
3.1 mins	4.5 mins	3.70×10^{-3}	Thorium C" Thorium Ω''	ThC" Th Ω''	208 208	81 82
.....	(Lead)	Pb ²⁰⁸

Note 1.—Thorium. The value given for λ is that obtained from the direct counting of the α -particles emitted by a compound of thorium. All the other values are less; the smallest being 0.55 of that given in the table and giving for $\theta = 3.45 \times 10^{10}$ years and for $T = 2.37 \times 10^{10}$ years (*Phys. Zeits.* 1918, 19, 259).

Note 2. Thoron is also called the thorium emanation.

Note 3. Thorium C undergoes a double disintegration: 65% of the atoms emit β rays and produce the substance ThC' which gives α rays, and 35% emit α rays and produce the substance ThC'' which gives β rays.

Mesothorium is easily separated from thorium. There is no doubt that the initial discovery of radiothorium in the thorium residues was not a result of the separation of radiothorium directly from the thorium, but of the separation of radiothorium which had grown in the interval from mesothorium. A day after separation a preparation of mesothorium shows a strong β and γ ray activity. —Sir E. Rutherford.

Commercial mesothorium is standardised by comparing the γ ray activity with that of a standard radium preparation.

α , β and γ ray activity in a specimen of mesothorium initially equal to 1 mg. of radium will increase in three years to the equivalent of 1.5 mg., and after ten years will again be equal to 1 mg. Consequently during this ten years it has an average activity equal to 1.2 mg. of radium. It will ultimately decay to about half the initial value after twenty years.

Mesothorium was at first believed to emit β rays, but later work has shown that this is due to the presence of a substance of quick period, which is produced by the mesothorium. This new product called mesothorium-2 emits only β rays, and has a half value period of 6.2 hours, as stated in the Table.

To Test Radium for Mesothorium. The simplest test is to heat it for a short time to drive off the emanation. The preparation must then lose its

SERIES
of Radioactive Elements—1923.

Isotope	Radiation	α_0	V	$\mu \beta \text{Al}$	$\mu \gamma \text{Al}$	$\mu \gamma \text{Pb}$	Notes
Th	α	2.58	0.0469	1
Ra	—
Ac	β and γ	$\left\{ \begin{array}{l} 0.37; 0.39; \\ 0.43; 0.50; \\ 0.57; 0.60; \\ 0.66 \text{ and } > \\ 0.70 \end{array} \right\}$	20.2 to 38.5	26; 0.116	0.62	...
Th	α (β)	3.67	$\left\{ \begin{array}{l} \alpha \text{ } 0.0527; \\ \beta 0.47; 0.51 \end{array} \right\}$
Ra	α	4.08	0.0546	2
Rn	α	4.74	0.0574
Po	α	5.40	0.0600
Pb	β and γ	$\left\{ \begin{array}{l} 0.63; 0.72 \\ (C + C'') 0.29; \\ 0.36; \\ 0.93 \text{ to } 0.95 \end{array} \right\}$	110	160; 32; 0.36	3
Bi	65% β	14.4
Po	α	8.16	0.0688
Pb
Bi	35% α	$\left\{ \begin{array}{l} 4.55 \\ 4.69 \end{array} \right\}$	0.0572	4
Tl	β and γ	(See ThC)	21.6	0.096	0.46	5
Pb

Note 4. Thorium C. The value $\alpha_0 = 4.69$ is that corresponding with $V = 0.0572$ which has been directly measured.

Note 5. Thorium C'' is also called thorium D.
For the meaning of the symbols T, α_0 , V, etc., see the data for the Uranium Radium and Actinium series, p. 684.

γ -radiating power after a few hours, completely regaining it only after the lapse of many weeks. Instead of heating it, it can of course be dissolved in water and the solution evaporated. If after the radium emanation has been driven off and the radium C has been destroyed (which takes a few hours) there is still some γ radiation, this is due to mesothorium. The ratio of the γ -radiation before and after the treatment is a measure of the proportion of radium and mesothorium in a mixture.—*J. Röntgen Soc.*, April, 1911; *J. chem. Soc. Abstr.*, ii/1911, 8.

Physical methods have also been employed but are complex owing to the similarity of the average penetrating powers of the γ rays from radium and mesothorium. They have the advantage that the tube need not be broken open.

The chemical similarity of radium and mesothorium forms an example of two elements of different radioactivity but *entirely identical* chemical character.

Mesothorium and radiothorium produce very marked effects on a zinc sulphide screen.

Ratio of mesothorium to thorium.—R. N. McCoy and L. M. Henderson (Abst.), *J. Röntgen Soc.*, April, 1919, 62.

Therapeutic Use of Thorium Degradation Products.

Mesothorium. Action on malignant growths is said to be "just like that of radium." Cancer of the tongue showed improvement. Psoriasis plaques are recorded to have been cured.—See also *Lancet*, i/1914, 418.

Malignant and non-malignant cases treated by introduction of mesothorium into the uterus in capsules.—*Brit. med. J.*, ii/1913, 923 (but burns have been caused by its use).

Thorium X. Has been injected into sarcomata and given intravenously in dose (?) of 1/100,000 mg. in 1 ml. of normal saline, but is dangerous and must be used with caution.

Myeloid leukæmia treated with thorium X intravenously, commencing with 50 electrostatic units and increasing the amount. Treatment continued for 9 months, during which 8,000 electrostatic units were given. The dose must be found experimentally in each case, the blood condition being an indication of amount required.—*Brit. med. J. Epit.*, ii/1924, 41.

Thorium X Poisoning has occurred from injections.

Thorium emanation.—Inhalations may be effective in the initial stage of chronic rheumatism. Three patients took daily inhalations, for 15 to 30 days, of 70 to 90 units. Treatment of no value in subacute and contraindicated in acute form. In cases with exostoses, intramuscular injections of thorium X are preferred.—*Per J. Amer. med. Ass.*, ii/1925, 153.

The following salts of thorium, by reason of their radioactivity, have found therapeutic utility.

Thorium Oxide. A heavy white powder insoluble in water and dilute acids. A suspension in liquid paraffin has been suggested for diagnostic purposes in X-ray work, to replace Beck's bismuth paste.

Thorium Pads, containing **Thorii Hydroxidum**, $\text{Th}(\text{OH})_4$, have been made to fit the part affected, e.g., head, spine, etc. For use in nerve affections.

Thorii Nitrates, $\text{Th}(\text{NO}_3)_4$. White crystals—usually in commerce with water of crystallisation. Apart from its use in the mantle industry is employed for producing thorium X and the emanation inhalation.

Soluble in water 1 in less than 1; in alcohol 1 in 5. Exsiccated salt is soluble to the extent of $2\frac{1}{2}$ in 1 of water.

Thorii Chloridum, $\text{ThCl}_4 + 8\text{H}_2\text{O}$, and **Thorii Sulphas**, $\text{Th}(\text{SO}_4)_2 \cdot 4\text{H}_2\text{O}$. White crystals—the former soluble in water—the latter slightly so.

TYPHOID and PARATYPHOID and other intestinal affections well treated by thorium sulphate at the rate of 4 g. *per diem*, either in form of 2% solution or in cachets. Effects said to be most marked.—*Paris méd.*, 1917, 7, 398. See also *Prescriber*, Jan. 1918.

Thorii Oleas. Thorium hydroxide 300 will interact with approximately 1120 of oleic acid. A little ether is added to dissolve the oleic acid. The salt is at first pasty, ultimately becoming hard. Suggested for use in the form of an ointment with paraffin basis for eczema.

Unguentum Thorii Oleatis (Drage). Contains 25% thorium oleate rubbed into a smooth cream with almond oil. Used with marked success in old chronic psoriasis, eczema rubrum, gouty eczema, and in boils and carbuncles. Sycosis has been cured with a few applications.

URANIUM AND ITS DISINTEGRATION PRODUCTS. It was shown by Sir William Crookes and M. Becquerel that from uranium salts, by chemical processes, a small amount of substance (then called uranium X), could be isolated, which was responsible for the whole of the β ray activity. The salts freed from this uranium X gradually and completely recovered their power of producing β rays, so that the uranium X was formed by the decomposition of uranium.

It has since been found that the disintegration is rather more complex, uranium X itself not being a simple substance. By loss of a helium atom (α ray) uranium I (238) is converted to uranium X_1 (234), which has a half-life value of 24.6 days. This gives rise to β rays, changing to uranium X_2 (234), also called brevium, which has a period of only 1.15 minutes, a further loss of β rays giving uranium II. This is related to radium through polonium, and it seems probable that either uranium I or uranium II gives a branch chain containing the actinium series.

For further data regarding the products of uranium see the table for the uranium and radium series, p. 684.

Uranii Acetas. Small yellow crystals with odour of acetic acid. Employed principally in chemical analysis, e.g., estimation of phosphoric acid, cf. Urine Analysis.

Uranii Nitrates. Lemon-yellow prismatic crystals. Soluble in water 2 in 1. Taste astringent.

In psoriasis and senile atrophy of the skin, lotion of this salt 20 grains to the ounce useful combined with uranium oxide ointment.—A. Clark, *Brit. med. J.*, ii/1912, 716.

X-RAY DIAGNOSIS

X-rays, or Röntgen rays, were discovered by Röntgen in 1895. They are similar in nature to light, heat and wireless waves but of considerably shorter wave-length, those used in X-ray diagnosis having a wave-length between 0.6 and 0.124 Angstrom units.

Method of Production. They are produced in medical practice in an X-ray tube. A modern X-ray tube is a vacuum tube and contains a filament which is heated red hot. Opposite the filament is the target, which consists of a piece of tungsten mounted on a block of copper.

The filament is made negative, relative to the target, by the application of a suitable high voltage, with the result that the negatively charged electrons travel from the filament to the target. Here they are stopped abruptly, with the consequent generation of much heat (which is dissipated by a cooling system) and also of X-rays.

The region where the X-rays could escape through the glass of the tube is usually surrounded by lead in which a small window is left, so that the emergent beam is confined to a definite direction (so called "self-protected" tubes).

The electrons from the filament are focussed on the target, so that only a small area on this is used for the production of X-rays. Tubes are often rated according to the size of this focal spot, a fine focus tube having an effective area of less than 2.2 sq. mm., medium focus tubes being about 3.1 sq. mm. and broad focus 4.1 sq. mm. or more. They are also rated according to the number of watts (milliampere \times kilovolts R.M.S.) which can be applied to the target for one second. The above-mentioned focal spots

would correspond approximately to 2·5 kw., 6 kw. and 10 kw ratings, with fixed target tubes.

Sometimes the targets are made to rotate and then the electron stream strikes a different part of the tungsten target each moment. These tubes have a much higher kw. rating for a given sized focal spot. Tubes may now be obtained in earthed metal casings and with suitable shock-proof leads, so that danger from electric shock should no longer be present.

Accessory Apparatus. A suitably regulated transformer is required to raise the voltage of the A.C. mains from 100 to 480 volts, according to supply available, to between 40,000 and 100,000 volts, the figure being regulated according to the part being radiographed.

Other controlling devices required are accurate timing devices with control ranging from 1/100 second to 10 seconds in powerful sets, and 1/10 second to 10 seconds in smaller sets. Arrangements are made for the suitable control of the filament current, which in turn controls the current through the tube.

A large set will take from 12 to 30 kw. for one second from the main supply and usually requires a special mains cable. Small mobile units can be worked off ordinary power plugs and will take about 3 kilowatts or 15 amperes on a 200 volt A.C. supply. Three-pin plugs, with one pin for earthing, should always be used.

Portable X-ray Units. Small portable sets are available to work off electric light supplies, but are, of course, very low powered. They are of use for fracture work in the patient's home and some chest work, but if a more powerful set is required complete units are available in London generating their own electricity. Amongst others may be mentioned the Order of St John and the British Red Cross Mobile X-ray Department, 12 Grosvenor Crescent. Films taken by them may also be sent to the British Institute of Radiology for interpretation by senior radiologists.

Cineradiography. A method of examining the movements of joints and organs of the living body by taking a photograph of the screen image with a cinematograph camera.

To obtain a sufficiently brilliant screen image to record on a cinematograph film in the fraction of a second one must employ an X-ray plant giving sufficient output, and an X-ray tube capable of withstanding the heavy currents that are necessary for the production of a powerful beam; the camera lens must have as large an aperture as possible to allow the maximum of light to pass through it; the film employed must be sensitive to the particular wave-length of light emitted from the fluorescent screen used; it is necessary to cut off the direct beam of X-rays passing through the screen, so that only ordinary light can reach the film; protection must be provided for the patient so that he will not suffer from undue exposure.

The advantages of cineradiography are: it enables one to obtain a rapid, inexpensive and permanent record of the functioning of active organs; the continuous "band" enables one to study movement for an indefinite period; the permanent records of movements may be used for diagnostic purposes, comparison with former records, teaching purposes, transmission abroad or elsewhere for obtaining specialists' opinion, or for information as to the condition of the patient in the past. (A description of the apparatus and the technique involved).—R. J. Reynolds, *Brit. J. Radiol.*, N.S., 1934, 415; *Brit. J. Radiol.* (Röntg. Soc. Sect.), 1927, 33.

Properties of X-rays.

(a) *Penetration.* X-rays have the power to penetrate matter to a degree which is dependent upon the quality or wave-length of the ray and the density of the material. The shorter the wave-length of the ray the greater the degree to which a given material is penetrated by it; and the denser the material the lesser the degree to which it will be penetrated by a given wave-length. Hence the possibility of X-ray photography, the rays being transmitted by the different structures of the body in different degrees dependent upon their several densities.

(b) *Absorption.* The fraction of the radiation which is not transmitted through the object irradiated is said to be absorbed. Such absorbed radiation is capable of producing:

(c) *Biological effects* in the animal body. (See section on X-ray treatment.) Certain chemical changes may also be induced in suitable media, among the most important of which are:

(d) *Photographic effects* and

(e) *Fluorescence.* The best known substance in which fluorescence is produced by X-rays is barium platinocyanide which is employed in the manufacture of fluorescent screens.

Fluorescent Screens. Certain substances give off visible light when exposed to an X-ray beam and hence, where differential absorption occurs, an image can be seen on such a screen, e.g., radio-opaque barium in the alimentary tract. Zinc sulphide or calcium tungstate are used, spread in a thin layer on cardboard. This should then be covered with a lead glass which will let the visible fluorescent light through but absorb the X-rays. The glass should absorb X-rays to the same extent as 2 mm. of lead would do.

“**Fluorazure**,” a new intensifying screen, allowing more rapid X-ray exposures, is made from specially refined zinc sulphide, and gives an intense azure blue fluorescence. Cadmium tungstate screens made it possible to reduce the ordinary exposure time to about 1/10th, but with fluorazure this could be reduced again to about 1/3rd or 1/5th the exposure with the tungstate screen.—N. S. Finzi, *Brit. med. J.*, ii/1932, 980.

Protection in Radiography. *Recommendations of the X-ray and Radium Protection Committee.* 1. No person should be employed as an X-ray or radium worker whose blood (as tested by a complete blood count) or general health is unsatisfactory. 2. Before beginning work or training the normal leucocyte level should be found. If none of the total counts reaches 6000 per c.mm. and none of lymphocyte counts reaches 1200 per c.mm. the worker should not be accepted. 3. Periodical total and differential blood counts should be made during the morning period every 6 months in X-ray workers and every 3 months in radium workers. 4. If there is a decided and sustained drop in the total leucocyte or lymphocyte count the worker should cease work and be placed under treatment, and every care taken on resumption of work to prevent a recurrence.—*Brit. med. J.*, ii/1933, 838.

Recommendations by the X-ray and Radium Protection Committee for electrical precautions in X-ray rooms.—*Brit. med. J.* i/1934, 294.

All persons working with X-rays should consult the above recommendations, copies of which can be obtained from the British Institute of Radiology, 32 Welbeck Street, London, W. It should be remembered that although tubes are described as "self protected," this is only a relative term, and the operator should avoid exposing himself to any part of the direct beam. It must also be remembered that there is considerable scattering of the primary beam from the patient, and it may be necessary to protect the operator from such scattered rays.

The operator must have sufficient knowledge of his apparatus and X-ray dosage to avoid giving a dangerous or excessive dose of rays to the patient, whether while screening or by an excessive number of exposures. He should also beware of conducting prolonged X-ray examination on any patient who has been previously X-rayed within 14 days or has had, within some months, heavy dosage X-ray treatment to the part being radiographed.

Using self-protected tubes with $\frac{1}{2}$ mm. filter of aluminium, and working at a tube-patient distance of 24 inches and with a kilovoltage of about 80 k.v.p., 1500 milliamperere seconds is a safe dosage. This would allow 5 minutes of screening at 5 ma. At 12 inches one could screen safely for $1\frac{1}{4}$ minutes, the dosage of X-ray varying as the square of the distance.

For diagnosis, using less than 110 k.v.p., protective material should be of 2 mm. lead or equivalent to this; other materials in use being lead glass for the front of the fluorescent screen or for the operator's window. Barium plaster may be used for walls.

About 20 mm. ($\frac{3}{4}$ inch) of steel plate found to give protection equal to 3 mm. of lead. A barium sulphate mixture required 60 mm. to equal 3 mm. of lead. P. J. NEATE'S formula, one-third coarse barium sulphate, one-third fine, one-third cement, gave somewhat better results. The open lead-glass bowl affords no protection in many directions. Sheet-glass, of lead value 0.12 per mm., was spoken of—obtainable as thick as 18 mm.—G. W. C. Kaye and E. A. Owen. *J. Röntgen Soc.*, 1923, 169.

An exhaustive study of protective materials at the Nat. Phys. Lab. for the Protection Committee. Numerically, 1 mm. of the following is equivalent to the stated thickness of sheet-lead in mm.

Lead glass	..	0.12 to 0.2	Woods	..	0.001 or less
" rubber	..	0.25 to 0.45	Baryta plaster	..	0.05 to 0.13
Bricks and concrete	about	0.01	Steel	..	0.15

These are relative to tungsten X-rays generated by 100,000 volts.—G. W. C. Kaye, *Phys. Soc. and Röntgen Soc. Joint Publicn.*, Feb. 23, 1923.

Protection from scattered rays need not be quite so heavy; (1 mm. lead equivalent being recommended) which will apply to lead rubber aprons, etc. Lead rubber gloves must, unfortunately, be pliable and so are also of less protective value.

Protective materials and equipment can be tested by the National Physical Laboratory on request.

Nitrous acid is certainly not present in the air of the X-ray room in sufficient amount to produce ill effect upon the patient or operator. However, under favourable conditions ozone may be produced in amounts as much as seven

times as large as Konrich's figure for the minimum quantity (0.5 mg. per millilitre of air), which produces exhaustion, blood changes, etc.
Röntgen "gas" poisoning resembles ozone poisoning.—*J. Röntgen Soc.*, 1921, 155.

Photographic Aspects. Most modern films are duplitised, i.e., coated with emulsion on both sides. They are now made with the usual clear base, or with a blue base, giving a bluer tint to the unexposed parts in a developed film.

Films are also made with a matt base, which is of use to those without adequate viewing boxes, but the fine detail is not quite so clear as with the other two.

In order to be able to give rapid exposures, films are packed and exposed between intensifying screens which, by glowing like a fluorescent screen, enhance the direct effect of the X-rays on the film by a light effect. The only disadvantage is a slight loss of fine detail and hence, for limb work, plain films are often preferred.

Intensifying screens are made of cadmium or calcium tungstate or zinc sulphide.

Films are supplied in light-proof covers (double-wrapped) or in boxes (single-wrapped). They are taken out of their covering in the dark room and placed between the intensifying screens, which are kept in a special holder called a cassette, which is light-proof when closed.

Paper. Instead of using the sensitive emulsion on a celluloid base, it can also be obtained on a thick paper. These paper films are less expensive than ordinary films, and are of use for certain types of work where very fine detail is not required, e.g., barium meals and repeat fractures.

They may be used with or without intensifying screens, and are developed in the same way as X-ray films. When used with intensifying screens, only one screen is necessary since the emulsion is only on one side of the paper.

Developer for X-ray Films. Hydroquinone 320 gr., potassium bromide 200 gr., metol 80 gr., sodium sulphite (crystals) 16 oz., sodium carbonate (crystals) 8 oz., water up to 80 fl. oz.

Films should be developed for 5 minutes at 65°F. The solution will keep for some months. A 3-gallon tank will develop 200 films, taking a mixed batch of all sizes.

Fixing Bath for X-ray Films. Sodium hyposulphite 1 lb., potassium metabisulphite 1 oz., water 40 fl. oz.

A film should be fixed in a few minutes and shows no yellow emulsion on it when fixed. Films should be washed in running water for half an hour after fixing.

Contrast Media. A detailed radiographic image can only be obtained where differences of radio-opacity occur.

Cartilage is so similar in radio-activity to skin and muscle, that normally it cannot be seen as a separate shadow. In order to make the hollow viscera visible, contrast media are introduced into them and hence they can often be outlined.

The following are some of the contrast media employed:—

Alimentary Tract. Barium sulphate.

For the oesophagus. A thick paste made of pure barium sulphate and water is very satisfactory. A tablespoonful of the paste is placed in the patient's mouth, and he is then requested to swallow it, the operator watching its passage on the fluorescent screen. If the patient complains of great difficulty in swallowing it is safer to use the barium emulsion as for the stomach, as the thick paste may stick and cause complete obstruction for a time if there is much œsophageal narrowing.

Stomach and Duodenum. Pulvis Barii Sulphatis Compositus (B.P.C.).

A good alternative formula for barium meal work is:—Barium sulphate 10 oz., vanillin 2 gr., saccharin 2 gr., tragacanth 60 g., distilled water to 20 fl. oz.

The gum and barium should be mixed as a powder, and then water added gradually.

The usual technique is for the patient to swallow a mouthful of the mixture and the mucosal pattern of the stomach is then examined. Later the stomach is filled out with barium, and an adult may require 15 to 30 oz. of the emulsion. No food or drink should be taken for 6 hours before a stomach examination.

For children, some prefer bismuth oxychloride, but the barium emulsion diluted half strength with water is quite suitable. Only a small quantity is given and the only danger is stagnation in the colon. If followed by a purgative after a suitable interval this danger can be avoided.

Small and Large Intestine. The above emulsions are suitable.

Barium Enema. Barium sulphate 6 oz., tragacanth 40 g., water to 20 fl. oz.

Or the barium meal emulsions may be used diluted with water.

The stomach can be outlined to some extent by giving a seidlitz powder and outlining it by carbon dioxide (low density contrast media) and the colon by air inflation.

Urinary Tract. For retrograde pyelography, radio-opaque catheters should be used, and a sterile 20% solution of sodium bromide or 15% sodium iodide can be injected up the catheters to outline the renal pelvis or ureters.

The normal renal pelvis holds 5 to 15 ml., while a large hydronephrosis may require 100 ml. to outline it. If large quantities are used, they should be drained out before the catheter is withdrawn. The bladder may be outlined with 10% sodium bromide. Occasionally, negative contrast media (air or oxygen) are used to demonstrate the renal pelvis.

Thorotrast, a stabilised thorium dioxide sol containing 25% of thorium dioxide, diluted with water or physiological salt solution, is used in retrograde pyelography in a dilution of 1 in 2; in cystography, 1 in 5; and in examination of tracts of fistulæ, 1 in 1.—*Brit. med. J.*, ii/1932, 112.

Intravenous Pyelography. Uroselectan "B" or Per-Abrodil, when injected intravenously, are secreted rapidly by the kidneys and give good shadows of the renal pelvis, calyces, ureters and bladder.

Adult dose: 20 ml. Uroselectan "B" is non-toxic and non-irritant to the tissues. Should not be used in uræmic patients.

The patient should restrict fluid intake for several hours before, and no diuretics, such as tea or coffee, should be taken for 12 hours. First skiagram taken 2 to 5 minutes after injection.

Sixty per cent. will be excreted in the first half hour, if the kidneys are functioning normally.

For further references to Uroselectan "B" and Abrodil see Vol. I, pp. 877 and 769.

Gall-Bladder. Sodium tetraiodophenolphthalein, when in the blood stream, is secreted in the bile by the liver. If it reaches a normally functioning gall-bladder, it is stored and concentrated, and outlines the gall-bladder on a subsequent radiogram.

Intravenous injection. Dose: 3.5 g. in 10% solution in sterile water (i.e., 35 ml.).

It is very toxic locally and care must be taken that none escapes into the tissues during injection.

The patient should have no food or drink after supper in the evening. The injection is given early next morning and films are exposed 4 and 8 hours later.

Oral method. This is now almost as accurate as the intravenous method, 98% of normal gall-bladders producing a good shadow, and it is, therefore, usually the method of choice.

Dose: 3.5 to 5 g. dissolved in an acid medium.

The patient takes a fat-free supper at 7 in the evening and the dye is best taken directly after in half a wine glass of grape or orange juice. No further food or drink should be allowed until after the films are taken, about 15 and 17 hours later. Sometimes a final film is taken an hour after a fatty meal to see how the gall-bladder is emptying, or to detect small stones in it.

Contra-indications. Severe liver disease or marked obstructive jaundice. In cases of gastric or duodenal ulcer, non-filling is not a conclusive indication of a lesion in the biliary tract, if the gall-bladder fails to fill with and concentrate the dye.

For further information concerning the diagnostic use of sodium tetraiodophenolphthalein, see Vol. I, pp. 674-679.

Genital Tract. Iodised oils, e.g., Lipiodol, may be used, by injection into the uterus, to outline the uterus and fallopian tubes. Pregnancy is a contra-indication.

They may also be injected into the seminal vesicles, but the method is not much used in this country.

Peritoneum. Oxygen may be injected into the peritoneal cavity, which is then radiographed. This procedure is mainly used for localisation of abdominal tumours, where other methods have failed to give the desired information.

Spleen and Liver. Thorotrast, when injected intravenously is absorbed by the liver and spleen, and these become dense radiographically. It may demonstrate large secondary deposits in the liver, as it is not absorbed by these.

Dose: 10 ml. first day; 15 ml. second day; 20 ml. third day and then to a total of 50 to 75 ml.

Although death has rarely occurred as a result of Thorotrast, it is reasonable to suppose that even such a feebly radio-active substance as thorium must have some effect. It has been shown that the liver and spleen are still easily visible radiographically 2½ years after administration of Thorotrast.—W. P. A. Murphy *Brit. med. J.*, ii/1933, 249. Use unjustifiable except in malignant disease with hopeless prognosis.—J. F. Brailsford, *ibid.*

Dangers of faulty diagnosis due to retention of remnants of thorium, trace being found in the kidneys up to 2 years after pyelography.—K. Scheele, *p. Brit. med. J. Epit.*, i/1934, 30. The delayed effects of Thorotrast: a warning against its employment.—*ibid.*, 40.

Trachea and Bronchi. Iodised oil, e.g., Lipiodol, can be introduced by several methods:—Puncture through crico-thyroid membrane, laryngeal catheter via nose, or simply dropped on back of tongue after anæsthetising with cocaine spray; also down bronchoscope during bronchoscopy.

For a full description of these various diagnostic procedures using Lipiodol, see this vol., p. 132; see also Vol. I, p. 515.

Dose: 10 to 20 ml. depending on the regions which it is required to fill at a sitting.

Pleural Cavity. Artificial pneumothorax is sometimes used for diagnosis of suspected innocent tumours (fibroma of chest wall). After empyema, Lipiodol may be injected via the sinus to see that the cavity is closing up well.

Lipiodol is also used to outline the parotid duct and its branches and the submaxillary and lachrymal ducts.

Nasal Accessory Sinuses. Lipiodol, Campiodol or Brominol. Brominol is lighter than Lipiodol.

Spinal Theca. 1 to 2 ml. of Lipiodol injected by passing needle into cisterna magna via space between atlas and occiput.

Examination conducted with the patient sitting up. May also be injected by ordinary lumbar puncture, but a lighter oil base used so that opaque material floats upwards.

Skull. Air may be injected by lumbar puncture or directly into the cerebral ventricles via a small trephine hole, and the cerebral ventricles can thus be outlined on a radiogram.

Arteriography. Thorotrast, 10 to 20 ml., to outline arteries to limbs or brain. Rapid skiagram taken during injection. Veins may also be outlined by this means.

Sinuses. May be outlined with Lipiodol, or suspensions of bismuth oxychloride. Lipiodol tends to drain away better.

Joints. These are sometimes outlined by oxygen or Uroselecta "B" injected into the synovial space.

X-rays are also used without the help of contrast media for the examination of the bones, muscles and viscera, etc., and for the localisation of radio-opaque foreign bodies. It should be noted

that glass may contain some lead and is then opaque, or may be of a density so near to the skin and muscle that it cannot be demonstrated by X-rays.

The teeth are best examined by special small dental films, which are placed in the mouth and held against the teeth either by the patient's own forefinger or by special dental holders.

A skiagram gives only a two-dimensional image, and where possible, a view at right angles should be obtained to give a composite three-dimensional view of the part. Where this is not possible, stereoscopic films can be taken. Two films are taken, the tube being moved $1/10$ of the tube-film distance between each film. The films are then viewed in a mirror stereoscope, or with stereoscopic binoculars. The method entails judgment on the part of the observer and is not as good as two films at right angles, where these can give the required information.

Legal ownership of X-ray films. It is almost certainly the custom that the films remain the property of the medical man who takes them or under whose direction they are taken. Although many radiologists recognise an informal right in the patient to have the films lent to a practitioner, who may at a future time have charge of his case, for his guidance in its treatment, it is unlikely that the patient could enforce such a right at law.—*Brit. med. J.*, i/1934, 83.

There are very few radiologists who do not send either a film or a print to the patient's doctor and a very large proportion of the patients are subsequently presented with the films. It is probable that a court of law would find there was no universally accepted custom or that it was usual for the patient to be presented with his films.—C. H. C. Dalton, *ibid.*, 172.

Industrial uses of X-rays. The examination of materials by X-rays has developed to tremendous proportions. Various methods are used, such as direct radiography, investigation of the crystalline structures of materials by X-ray diffraction methods, and the study of the X-ray spectra emitted when the materials under investigation are made the targets of the X-ray tube.—Clark, *Applications of X-rays*.

X-rays were used for revealing defects in aeroplane timber—wood is very transparent to the rays.—G. W. C. Kaye and R. Knox, *Chem. & Drugg.*, 1919, 537. See also *Brit. J. Radiol. (Röntg. Soc. Sect.)*, Apl., 1926, 67.

Metal Radiography as worked at the Research Dept. at Woolwich. Among other applications, is the estimation of the amount of a heavy element alloyed or mixed with a lighter, e.g., the quantity of lead present in different specimens of brass. An ionisation method, or a simple electroscope, may be used.—W. J. Wiltshire, per *J. Röntgen Soc.*, Oct. 1933, 155.

X-ray examination of coal, with description of a unit for making examinations.—C. Norman Kemp, *J. Röntgen Soc.*, Oct. 1924, 174.

X-RAY AND RADIUM THERAPY

Radiations have proved valuable mainly in two sets of conditions : (1) In acute and chronic inflammatory conditions; (2) In the treatment of new growths, especially the malignant variety.

The mode of action of radiations in causing the resolution of inflammatory conditions is not clear. In doses applicable to the human body they have no effect on bacteria. It has been suggested that in acute inflammatory conditions the rays, by affecting a much wider area than is involved in the inflammation, stimulate the production of non-specific antibodies on a larger scale than would be the case with the limited inflammatory lesion

alone. In chronic inflammatory conditions, the mode of action may be by causing the dissolution of the accumulations of small round cells which characterise these conditions, thus allowing a more active hyperæmia, i.e. a mild acute inflammatory reaction. The repeated application of the radiations at intervals of several days, by causing these repeated mild inflammatory reactions, tends to overcome the infecting agent.

Considerable difference of opinion exists as to the mode of action of radiations in malignant disease. By some authorities the effect is regarded mainly as an indirect one, but there is no little doubt that in the majority of cases the direct damage to the cancer cell is of greater importance, at any rate in so far as the immediate result is concerned. The value of radiations in the treatment of cancer depends upon the greater sensitivity of the cancer cells in relation to the normal body cells. This may be due to the much greater activity of the cancer cells compared with the normal cells. Such a view is supported by the fact that the normal body cells themselves exhibit a degree of sensitivity which is roughly proportional to their activity. Thus, the essential testicular and ovarian cells and those of the skin, which are constantly renewing themselves, are among the most sensitive cells in the body.

Constitutional Effects [of X-Ray Treatment].—The term “X-ray sickness” is applied to the “symptom complex” which may follow the application of X-rays in moderate or large doses. It occurs most commonly after the irradiation of the upper abdomen, but it may also occur after the irradiation of any other region if the volume of tissue exposed has been sufficiently great. In its lesser degrees, the condition is characterised by a feeling of malaise, headache and nausea. Severe degrees are accompanied by vomiting, which may be severe and even intractable. In the worst cases, continued vomiting may lead to the exhaustion and death of the patient. The causation of the condition is obscure, but it is probably in the nature of protein poisoning due to the liberation of the products of cell destruction. The condition in its milder forms is treated by the exhibition of gastric sedatives such as bismuth and hydrocyanic acid, or tincture of iodine. In the more severe degrees, chlorbutol or even morphine may have to be given. In the worst cases benefit has been claimed from the infusion of normal saline into the veins.

X-ray sickness successfully treated with liver extract intramuscularly, from 1 to 4 ml. (1 ml. usually sufficient). The effect lasts 2 days.—J. H. D. Webb *Brit. med. J.*, i/1934, 15.

Effects of Radiations on Normal Tissues

Skin. After a sufficient dose of radiations has been applied to the skin, an erythema or reddening is observed. This reddening appears only after a latent period of several days has elapsed. The latent period varies with the quality of the ray, being shorter with

the softer rays, i.e. those of longer wave-length, and longer with the harder rays, i.e. those of shorter wave-length. The minimum latent period is a few days, while the maximum may be 3 or even 6 weeks. The erythema varies with the dose applied, from a faint pink colouration to a dark bluish-red, and its limits follow exactly in shape and extent the area to which the rays have been applied. The appearance of the erythema is accompanied by epilation, but unless very large doses have been given so as to produce destruction of the hair follicles, regrowth of the hair is constant. The erythema passes off after a few days and is followed by pigmentation and by desquamation of epithelium. With larger doses, blisters, bullæ and even deep ulcers may be produced; the latter are extremely painful, show little tendency to heal, and may even prove fatal. Late changes in the skin may occur after intensive irradiation, even after an interval of months or years. These include telangiectases and ulcerations, which may be very intractable. Permanent damage to the skin, in the form of thickening and abnormalities of pigmentation, is not uncommon.

The dosage required to produce these various degrees of reaction is well known and can easily be repeated, and a unit has been formulated using a moderate grade of erythema as a standard. This is known as the "Erythema Dose" (E.D.) or the "Unit Skin Dose" (U.S.D.).

Blood. All the formed elements of the blood are affected by radiations. Of these the leucocytes are most affected, especially the lymphocytes. The red cells and hæmoglobin are only severely affected in cases in which some degree of anæmia exists at the commencement of the radiation treatment.

Mucous Membranes. The mucous membranes of the mouth, throat, intestine, bladder and rectum, may all undergo inflammatory changes after intensive irradiation. These changes present the ordinary characteristics of inflammations affecting these various organs. They are frequently produced in the treatment of malignant disease, and if the dosage has been correctly gauged they are only transient.

Generative Organs. Sterilisation may be produced in both male and female as a result of exposure to X-rays or radium, either for therapeutic purposes, or from accidental exposure over a long period in the course of employment. In either type of case, the condition is curable, at least in a proportion of cases.

Lungs. Severe damage to the lungs can be caused by X-rays. This damage takes the form of an acute pneumonic condition, or chronic fibrosis with bronchiectases. These injuries were formerly fairly common after the treatment of malignant disease in the breast, but with the use of modern technique in treatment they are now rarely seen.

Nervous System. The nervous systems, both central and peripheral, are very insensitive to X-rays, and are not appreciably affected by clinical dosage.

The Treatment of Radiation Effects.—For the erythema of the skin little treatment is required. Irritation may be allayed by a simple starch powder during the treatment, and by a zinc oxide, bismuth and starch powder after the treatment. Preparations containing heavy metals must *not* be used during the treatment, since the secondary radiations produced from them may cause severe damage. For blisters and small bullæ, Cycloform ointment 5% may be employed; or, when larger areas of skin are involved, flavine in paraffin 1/4000 may be used, but spirit must not be used in making up this preparation.

Treatment of Late X-ray Effects. Late X-ray effects are of great rarity. Telangiectases may occur from 1 to 3 years after X-ray treatment (less frequently with radium). Other effects are atrophy of the skin, thickening of the skin, skin cracks, benign or malignant neoplasms, late ulcerations, and acute inflammation of the subcutaneous tissues; the treatment of the last two conditions is complete rest and protection of the part, even immobilisation in plaster—in the early stage a vaccine from a culture of the organisms might give rapid recovery. Telangiectases are sometimes removed by high frequency or the static machine; cracks in the nails yield to a cellulose solution; warts can be treated by paring or rubbing down with emery paper.—*Brit. med. J.*, ii/1932, 1116.

Desitin-Röntgensalbe. An ointment with a basis of pure cod-liver oil. Very effective for the treatment of late X-ray effects, such as relief of the tightness of the skin and the unpleasant cracks.—Stanley Melville, *Brit. med. J.*, ii/1932, 1116.

X-Ray Dosage.—Various methods have been used for the measurement of X-rays. Of these all are now obsolete with the exception of the ionisation methods. The latter depend upon the effects of X-rays on the electrical conductivity of the air, the air becoming ionised and consequently conductive of electricity to a degree which is dependent upon the intensity of the source of the radiation.

The method devised by Dr. Sievert, Director of the physical laboratories at Stockholm, Radium Lemmet, consists in the use of small spherical electroscope condensers, charged from a suitable source, which are introduced into both cavities, the charge being determined before introduction and after exposure to the radiations *in situ*. The use of a delicate electrometer is entailed, but the individual condensers, after withdrawal, can be packed and sent to the physical laboratory for measurement.—*Brit. med. J.*, ii/1932, 1062.

One other method of measurement of X-rays may be mentioned as it is still sometimes used in this country. It depends upon the effect of X-rays in changing the colour of barium platino-cyanide from apple-green to russet-brown, this change occurring after a given dose of X-rays has been administered. The barium platino-cyanide is coated upon small discs of pasteboard which can be exposed at a given distance from the source of the X-rays. This was one of the earliest methods of X-ray dosage measurement to be introduced, and is associated with the names of Sabouraud and Noiré.

The modern unit of X-ray dosage is the international "r" unit. The value of this unit in terms of biological effect varies somewhat with the method of measurement and the quality of the ray. With rays produced at 180 kv. and a 0.5 mm. Cu filter, the Erythema Dose is equivalent to 650 "r."

Other units that may be mentioned are the "H" unit (Holznecht) and the "B" unit (Sabouraud and Noiré), but these are only of historical importance.

Complete series of estimations of X-ray and radium dosage at various depths in the body under various conditions have been prepared, and are used in the treatment of deep-seated disease.

A very small margin exists between the dose which will determine a cure and the dose which will provoke an injury. Daily examination of patients is necessary: modification of the normal tissues and of the general condition by X-ray treatment sometimes appears so quickly that it is often necessary to diminish the daily dose or the size of the fields in the course of treatment. There is no fixed method of treatment but a simple clinical treatment for each individual patient and for the special type of tumour.—Henri Coutard, *Lancet*, ii/1934, 1.

Technique. X-rays of all available qualities are used in treatment. For the treatment of skin diseases, soft rays are used produced at 70 kv. to 100 kv. with no filter or with a light filter, e.g. 1 or 2 mm. of Al. In the treatment of conditions which are fairly superficial but which still require a ray of some penetration, higher kilovoltages (e.g. 150 kv.) with a heavier filter (e.g. 5 mm. Al) are used. The effect of the filter is to absorb the unwanted, less penetrating, portion of the beam. In the treatment of deep-seated lesions and of most cases of malignant disease, the hardest rays obtainable are used, produced at 200 kv. or more, filtered with 1 mm. or more of Cu. In these conditions, hard rays are used not only because of their penetrating power, but also because it is believed that the shorter wave-lengths have a more destructive effect on the cancer cell.

X-Ray Tubes for Internal Use. The British Thomson-Houston Company is the assignee of a tube patented by Coolidge for cavitary therapy. A very small cathode wire is enclosed in a focussing cup mounted in a fairly large metal cylinder, tapering to a small metal cylinder at the end of which is a heavy anode carrying a target set at 45 degrees. The rays are filtered through a window of chrome nickel steel. The tube is water cooled. A similar device made by the Siemens Company is being tried in Germany. The rays are stated to be well tolerated and no burns have been seen. A white scab, similar to that produced by radium, is produced after a time on the surface of the tumour. This type of tube is advocated for applying large doses to the parametria and pelvic wall.—*Brit. med. J.*, ii/1932, 764.

The 900,000 volt *Cascade X-ray* at the New York Memorial Hospital equals in radiation 600 g. of radium (the total world supply). The rays pierce $1\frac{1}{2}$ inches of lead. In general, the denser the part the higher the voltage used.

Treatment by Radium. The radium is used in the form of the bromide or sulphate, but the strength of the applications is expressed in terms of radium element, so as to procure uniformity. It is put up in metal containers which also act as filters. The thickness of the containers is in the great majority of cases sufficient to remove the alpha and beta rays, leaving only the gamma rays for the purposes of the treatment, although beta rays are still occasionally used in treatment. A thickness of 0.6 mm. of platinum is sufficient for practical purposes to remove the beta radiations. Thicknesses of 1 mm. or even more are, however, sometimes used, the effect of which is to remove part of the softer or less penetrating gamma radiation.

Radium Containers in current use comprise **Tubes, Needles, Plaques and Cells.**

Tubes. These are of platinum, hermetically sealed, usually 1 mm. thick. Any additional screenage can be added by enclosing in capsule screens. 10 mg. tube is often of about the following dimensions: total length 20·7 mm., external diameter 2·95 mm., length 15 mm. Tubes of all sizes are, however, used.

Needles are cylindrical, with an eyelet hole at one end and either a conic or triangular trocar point at the other. They are usually of platinum, with 10% of iridium for strength, 10% for the body of the needle and 25% at the point. The thickness of wall varies between 0·5 mm. and 1 mm. and even more. (See also Screens *infra*.) By embedding a number of these needles containing, e.g., 1 to 3 mg., cross-fire effect is produced. "*Linear intensity*" is a new factor, conveying the amount of radium per unit length of the needle. Some hold that 0·6 mg. per cm. length of needle is a safe maximum. Standard dimensions are now in use, e.g., for a 1 mg. platinum needle: total length 26·5 mm., external diameter 1·6 mm., length of chamber 15 mm., eyelet 5 mm. point and screw 6·5 mm.

Needles can be converted into tubes for use in cavities, and into plaques for surface use, by means of suitable applicators.

Needles are now often made by packing standard small platinum cylinders into an external platinum case. This ensures more even distribution of the radioactive materials and greater accuracy of amount. Materials having a mean atomic weight about equal to that of copper give best secondary β radiation.

For holding needles in position for surface irradiation so that the radium is at a constant distance from the skin, e.g. of the neck, some medium is necessary which can be moulded to the part. The material most commonly used for this purpose is *Columbia wax*, containing beeswax 100 g., hard paraffin, m.pt. 62° 100 g., pine sawdust 20 g., melted on a water-bath, and poured into trays of the required depth. The sawdust sinks to the bottom, giving a finely granular lower surface which is applied to the skin. (See Ward and Smith, p. 164.)

Plaques. For surface use, employing the soft β rays, Monel metal containing about 67% nickel, 28% copper, and 5% other metals, is used. The radium is spread in the shallow portion and fixed in position—over this is a face of the same metal 0·1 mm. thick. This absorbs approximately 50% of the primary β radiation. The apparatus is therefore durable and uniform and supersedes varnish and vulcanite. Monel plaques may be square, round, oblong or oval. "Double strength" plaques contain 10 mg. of radium element per sq. cm., "full strength" 5 mg., and "half strength" 2·5 mg.

Cells are similar to tubes, but generally without an eyelet, and may be used for minute amounts for building up applicators of desired radium content.

The term "**Applicator**" is now employed to cover various devices holding the container in therapeutic use.

Sheath Needles are similar to ordinary needles, but the points are screwed into the shaft and hence removable. One, two, or more, "removable cells" may be inserted.

Flat Applicators for Needles are of brass or German silver. These have windows and are made for holding 2 to 6 needles.

Needle Introducers, Prostatic Applicators, Uterine Sounds and Applicators for Antrum, Rectal, Vaginal and Oesophageal use are also available.

Screens of Lead of various thicknesses are used, e.g., 1 mm. thick, covered with rubber, allow practically only γ rays to pass.

Lead $\frac{1}{16}$ to $\frac{1}{2}$ mm. permits the "hard beta" rays to pass as well as the gamma rays. **Silver** 1 mm. absorbs 99% of the hard β rays and **Brass** 1·3 mm. absorbs the same amount. When the aim is to utilise β rays, the duration is relatively short that the γ ray effect is wanted. Screens are necessary to cut off the β rays because of their greater action on the superficial structure.

Platinum $\frac{1}{2}$ mm. screens off 99·9% of the primary β rays and enables the use of all γ rays.

Gamma radiation acts by dissolution and absorption, while beta radiation acts by destruction through necrosis, with consequent suffering to the patient. The importance of adequate screening.—Sir C. Gordon-Watson and Stanford Cade, *Lancet*, i/1929, 634.

The therapeutic effect of the gamma rays is due to the high speed electrons they set free from the tissues, chiefly as "recoil electrons."

The methods of radium therapy are divisible under three headings:—(1) Interstitial therapy; (2) Short distance surface therapy; (3) Telecurie or “Radium Bomb” therapy.

In *interstitial therapy* the needles containing the radium are inserted directly into the tissues containing the lesion to be treated.

In *surface therapy* the radium is used in the form of plaques of various shapes and sizes, which are placed upon the skin or at a short distance from it (a few mm. to from 2 to 3 cm.).

In *telecurie therapy* large masses of radium (1 to 5 grammes or more) are used at a distance of several centimetres from the surface.

In 1933 a special Radium Conference appointed by the Royal Colleges of Physicians and Surgeons reported that there was a field of usefulness for radiation from massive units of radium and recommended that a radium unit containing not less than 5 g. of radium element be established. 5 g. of radium having been loaned by the Union Minière de Haut-Katanga for the purposes of this research, with the promise of a further 5 g. if necessary at a later date, a representative governing body of seven members was formed to organise the research, the location being the London Radium Institute (see *Brit. med. J.*, i/1933, 28; ii/1933, 121).

Effects of Radium on the Tissues. These are not dissimilar from those described for X-rays.

Post-radiation care. Full therapeutic effect is not seen till 2 months after treatment and during that time there may be lassitude and anorexia, and, when large, highly cellular tumours are resolving rapidly, considerable constitutional disturbance. Transient œdema of the skin develops a week after completion of treatment, developing into a well-marked erythema, vesication, and even superficial ulceration, which does not subside for 6 or 8 weeks, and during this time a soothing local dressing must be used. After treatment of the mouth and upper air passages there is œdema and inflammation of the mucous membrane during the week following, the tongue later becoming coated with a yellowish diphtheroid membrane, under which healing takes place. During this time (about 8 weeks), the mouth should be irrigated at least six times a day, and smoking, condiments and sauces should be avoided. After-care of carcinoma of the cervix should be undertaken on the same general principles. If efficient douching is not undertaken an adhesive vaginitis forms in the upper half of the vagina.—Roy Ward, *Practitioner*, ii/1933, 513.

DISEASES TREATED BY RADIATIONS (X-Rays and Radium)

(I) *Non-malignant*

ACNE. Good results are obtained by X-ray treatment, small doses being applied weekly.

ACTINOMYCOSIS. When localised, this condition is often successfully treated by X-rays in association with the oral administration of iodine. Large doses are necessary.

ACUTE INFLAMMATORY CONDITIONS. Resolution of these conditions is often assisted by the application of small doses of X-rays at intervals of several days.

Of 855 cases of inflammatory affections, including boils, erysipelas, anthrax, sinusitis, mastitis, orchitis, epididymitis, otitis media, etc., treated with small doses of X-rays, 76% were cured without operation, 19% were doubtful, and 5% were failures. Dosage recommended: 10% to 20% of the erythema dose and exposure limited to a few minutes at intervals of 3 to 4 days. Earlier failures probably due to excessive dosage.—A. Plichet, *Pr. méd.*, Mar. 4, 1933, 349.

AMENORRHŒA. Good results have been claimed from the application of small doses of X-rays to the ovaries and pituitary gland.

ARTHRITIS. Considerable relief may often be obtained, especially when the disease is recent and is mainly peri-articular. The rays are applied weekly in moderate doses.

CORNS and CALLOSITIES. Excellent results are obtained by the application of large localised doses of X-rays or gamma rays.

ECZEMA. Sub-acute and chronic cases are suitable for X-ray treatment. Complete relief may be obtained, but recurrence is common. One or two sittings, with moderate dosage, may be all that is required.

EXOPHTHALMIC GOITRE. Good results are obtained by the application of moderate doses of X-rays to the neck weekly.

X-ray therapy should be given a trial in the large majority of cases, the results being considered at 3-monthly intervals, and those not showing adequate improvement sent for surgical treatment. In patients who, for financial or other reasons, cannot face more than a short absence from active life, an operation seems the treatment of choice.—C. S. D. Don, *Brit. med. J.*, i/1934, 748.

It is equally an exaggeration to say that either X-rays or surgery is the treatment of choice. Neither method effects a cure but both have their place. In favour of surgery however, it should be said that the results are obtained in a shorter fraction of the time required by radiological treatment.—G. Keynes, *Brit. med. J.*, i/1933, 673.

HODGKIN'S DISEASE (LYMPHADENOMA). This disease is incurable, but the local glandular swellings respond well to moderate doses of X-rays; although recurrence is the rule, life may be prolonged for several years.

In most cases of Hodgkin's disease and lymphosarcoma, rays of medium wave-length are distinctly preferable. Lymphoid cells are so sensitive to irradiation that a moderate quantitative dose of rays generated at 135 to 140 p.p.s. (kilovolts and filtered through 4 or 6 mm. of platinum (depending on whether the nodes irradiated are in the subcutaneous tissues or in the mediastinum or abdomen) is sufficient to induce marked regression of the hyperplastic nodes. Exposure of many areas to rays of this quality may be repeated several times without undue risk, when the intervals between courses of treatment are a matter of months. The effect of treatment is rapid reduction in size of the enlarged lymph nodes in the irradiated regions, dyspnoea is often relieved within a few days, and gastro-intestinal disturbances rapidly subside. Treatment may be so effective in the advanced stages. Even if the treatment does not notably prolong the life of the average patient, it controls the manifestations of the disease and relieves the symptoms.—A. U. Desjardins, *J. Amer. med. Ass.*, ii/1932, 1233.

KELOID SCARS. Excellent results are obtained by the application of full doses of X-rays or radium, sharply localised to the region of the scar.

LEUKÆMIA. The chronic forms of this disease respond well to X-ray treatment applied to the spleen, and the blood-picture may be restored to an approximately normal condition. Recurrence is the rule after a variable number of months, when temporary success may again be obtained by repeating the treatment. The disease is invariably fatal, although its course may be prolonged for several years.

MENORRHAGIA. This condition can be cured by X-rays applied to the ovaries in sufficient doses to cause sterilisation. The best subjects for treatment are those in whom menorrhagia occurs at the menopause, when the X-rays are used to expedite the natural atrophy of the ovarian cells. Except in cases of extreme urgency, X-rays should not be applied to the ovaries during the child-bearing age.

Radium is of great value in uterine hæmorrhage. One application of radium element to the interior of the uterus for 24 hours.—P. C. Fenwick, *Brit. med. J.*, ii/1929, 455.

MYOMA UTERI. This condition is treated on the same lines as those of menorrhagia.

NEURALGIA. Relief is often obtained, especially in the trigeminal and post-herpetic varieties, by the application of weekly doses of X-rays to the Gasserian ganglion and the posterior nerve roots respectively.

PRURITUS. This can often be cured by the weekly application of small doses of X-rays.

PSORIASIS. This is often successfully treated by X-rays, especially in cases which are not of long standing. Recurrence is frequent, but a complete cure may be obtained. Moderate doses are applied at intervals of several days.

RINGWORM OF THE SCALP. X-rays offer the only means of a complete cure of this condition. Sufficient dosage must be applied to the scalp at one sitting to produce complete epilation.

SYCOSIS. In this condition also, a cure may be obtained by producing complete epilation.

SYRINGOMYELIA. Some good results have been claimed for weekly applications of moderate doses of X-rays.

TUBERCULOSIS. When localised to glands, joints or skin, this condition may often be helped by the application of small doses of X-rays at weekly intervals.

TUBERCULOSIS MENINGITIS. Five cases in children completely cured by deep X-ray therapy, employing 162 kilovolts, 4 ma., with 0.25 of zinc and up to 3 mm. aluminium filter, 150 to 200 r. units, with a focal distance of 34 cm., applied to the base of the neck, and to the forehead and temporal regions, three to four applications being made with 1 to 2 days between the first two, and 3 to 4 between subsequent applications.—Prof. Z. von Bokay (Hungary), per *Lancet*, 1932, 894.

(2) Malignant. A malignant growth or cancer is a growth which if left untreated steadily extends, pressing upon and eating away the structures with which it comes in contact and eventually destroying life, either by the local damage it causes or by the formation of one or many secondary growths in other regions of the body. The two main varieties of cancer are *carcinoma*, arising from epithelial or covering tissues, and *sarcoma*, arising from connective tissues. Many varieties of carcinoma and some of sarcoma can be destroyed by adequate irradiation, either by X-rays or by radium. Often, however, even though the local growths can be destroyed, secondary deposits are subsequently discovered and these may be multiple and lead to the death of the patient. In many cases the best result is only obtained by a combination of X-rays and radium.

When X-rays are used in the treatment of cancer, only the hardest obtainable rays (i.e. the shortest wave-lengths) should be employed. This applies equally whether the growths are superficial or deep. As a general rule, the hardest rays obtainable are produced at 200,000 volts, and it is important that filtration should be adequate (not less than 1 mm. of copper).

Radio-sensitivity of malignant growths. (1) *Highly radio-sensitive* growths that can be made to disappear by a dose of radiations producing little or no damaging effects on normal tissues)—(a) small, round-celled and lympho-sarcoma; (b) seminoma; (c) some carcinomas of the breast; (d) some carcinomas of the ovary; (e) certain cerebral tumours—medulloblastoma. These should invariably be treated by external radiation, X-rays or telecurie therapy, preferably X-rays. (2) *Moderately radio-sensitive* (growths which can only be destroyed by a dose of radiation approaching fairly closely the maximum tolerance dose of the healthy tissues)—(a) round-celled sarcoma; (b) endosteal and chondrosarcoma; (c) some periosteal sarcomas; (d) most carcinomas of the breast; (e) carcinoma of the prostate; (f) carcinoma of the bladder; (g) certain palatal, pharyngeal and laryngeal growths—lympho-epithelioma; (h) hypernephroma; (i) carcinoma of the cervix; (j) of the corpus uteri; (k) of the ovary; (l) of the thyroid gland; (m) of the lip; and (n) of the skin. Interstitial radium is best for this group wherever possible, except in extensive (carcinoma of skin) or inaccessible areas, when X-rays, or X-rays followed by radium, may be used. (3) *Radio-resistant growths*.—(a) Carcinoma of rectum; (b) œsophagus; (c) tongue; (d) many laryngeal carcinomas; (e) some carcinomas of the breast; (f) and of the ovary; (g) carcinoma of the bronchi; (h) certain metastases in cervical glands, especially arising from carcinoma of tongue; (i) spindle-celled sarcoma and fibrosarcoma. In these interstitial radium is the treatment of choice, but the whole extent of the growth must be thoroughly barraged and with full dosage. X-rays rarely achieve more than some degree of palliation.—W. M. Levitt, *Brit. med. J.*, ii/1933, 678.

CANCER OF THE TONGUE, FLOOR OF THE MOUTH, AND TONSIL are best treated by interstitial radium therapy to the primary growth, with or without X-rays to the cervical gland areas.

CANCER OF THE PHARYNX AND LARYNX are usually best treated by X-rays.

Of 45 cases of lymphosarcoma of the mouth and tongue treated by X-rays 17% were alive both after 5 years and after 7 years. Of 46 cases of epithelioma of the tonsil and soft palate, 28% were alive after 5 years and 17% after 7 years. Of 77 cases of epithelioma of the larynx 28% were alive after 5 years and 27% after 7 years.

A voltage of 180 to 200 kv. used, a filter of 2 mm. Zn, 3 mm. Al, 1 cm. wood, a milliamperage of 4 and a distance of 50 to 60 cm. A constant potential machine used and the dose measured in "r": for radio-sensitive tumours the depth-dose measured from 3500 to 5000 r and for radio-resistant tumours 4000 to 5000 r or more. Results exactly measured by biological consequences—*radio-epithelioma* involving complete destruction of the germinal layers of the mucous membrane and production of a false membrane, destruction being complete in 13 or 14 days and the lesion healing on the 26th day; and *radio-epidermatitis*, involving loss of epithelial layers and denudation of the dermis, appearing in 26 to 28 days with healing 15 days later.

Cure of cancer by X-rays possible, but very difficult and still dangerous. Henri Coutard (Fondation Curie, University of Paris), *Lancet*, ii/1934, 401.

CANCER OF THE OESOPHAGUS has recently yielded very encouraging results treated by X-rays by a method introduced by Levitt (*Proc. Roy. Soc. Med.* 1934).

CANCER OF THE STOMACH AND INTESTINAL TRACT have so far not proved amenable to radiation treatment.

CANCER OF THE SKIN is very successfully treated, either by X-rays or radium. Treatment must be intensive and repeated.

Rodent Ulcers. 99% of successful results in early rodent ulcers with following technique. (1) Give a mild erythema dose of filtered radium γ rays to the whole of the affected area; (2) repeat dose after 6 weeks if naked eye evidence of growth remains, and if necessary a third curative treatment; (3) give two prophylactic doses at 6 weeks and 14 weeks after the last *curative* dose. Radium or radon may be used and either plaques or tubes, but tubes are better adapted. For small lesions use a tube containing 50 mg. of radium with a filter of 0.5 mm. of platinum; the tube has an active length of 15 mm. and active diameter 4 mm. and is covered with rubber. In oval lesions not more than 6 mm. across or 12 mm. long, the tube is placed exactly over the lesion; the dose, in a patient of 40 or 50, is from 65 to 70 minutes—the raised lesions are given longer than the flat ones. For circular lesions of not more than 7 to 8 mm. in diameter the tube is placed for 35 to 40 minutes in one direction and for a similar time at right angles. In older patients, the dose is slightly increased and in younger patients diminished. In larger lesions two or more tubes may be used and the dose reduced somewhat.—N. S. Finzi, *Brit. med. J.*, ii/1933, 137.

Of 1773 cases of rodent ulcer treated at the Radium Institute, 77% were definitely cured. Small lesions of the hypertrophic and flat types treated by plaques, using beta radiation and a short unscreened exposure, and for the larger growths gamma radiation in the form of surface or interstitial radiation.—Roy Ward, *Practitioner*, ii/1933, 501.

CANCER OF THE LUNG yields a very small percentage of palliative results.

CANCER OF THE WOMB (CERVIX AND BODY) is successfully treated by a combination of X-rays and radium.

The "**Stockholm technique**," with some modifications, is that generally used in this country for treatment of cancer of the cervix. It consists of placing radium (roughly 40 to 50 mg.) into the cervix and body of the uterus and into the vagina (60 to 70 mg.) on three occasions of 22 hours each with an interval of one week between the first and second and between the second and third, the filter used being 1.5 mm. platinum with a special pessary for holding the radium. M. Donaldson, *Brit. med. J.*, i/1934, 547.

CANCER OF THE PROSTATE AND TESTIS IN THE MALE gives a proportion of good results when treated by X-rays.

Some TUMOURS OF THE BRAIN are amenable to X-ray treatment.

In the case of SARCOMATA, the result of treatment is determined by the rate of the growth, rather than by the site of its occurrence. Thus, lymphosarcoma is extremely sensitive to X-rays in whatever region it occurs, while a fibrosarcoma is very resistant.

SARCOMA OF BONE yields only a small proportion of good results with X-ray treatment.

GENERAL REFERENCES TO RADIATION THERAPY

(a) Non-malignant

Actinomycosis well treated by X-rays, and in tuberculous lesions of all kinds the greatest success has been attained—dosage must be small in order not to destroy the tubercle—in cervical glands one-sixth of an erythema dose at weekly intervals. Acne and eczemas respond well to the same dosage. In enlarged tonsils in children, X-ray results were very satisfactory. Pelvic inflammation in women, especially when due to tubercle, could be cured, and ocular inflammation did well with small doses.—J. H. Webster, *Brit. med. J.*, ii/1932, 310.

(b) Malignant

Results obtained with a 4-gramme “bomb” at the Westminster Hospital.

(1) Proved squamous-celled carcinoma of the buccal mucosa, floor of the mouth, palate, tonsil, lateral pharyngeal wall, pyriform fossa, and extensive carcinoma of the larynx disappeared *in toto* with complete healing.

(2) Cervical and inguinal glands secondary to squamous-celled carcinoma, fixed and inoperable, responded in certain cases.

(3) Spheroidal-celled carcinoma of the breast, unsuitable for surgery or needling; disappearance of primary growth and axillary glands; inoperable tumours retrogressed to permit of surgical removal.

(4) Bone sarcomata, in the long bones and vertebræ; made to ossify and replaced by apparently normal bone tissues.

The best form of bomb would be one containing the radium only during the period of treatment, as there is no haste on the part of the attendant to get out of the treatment room and the bomb can be placed carefully and accurately in position; it can also be much lighter as the lead upper half (required for protection of attendant making adjustments) can be removed.—H. T. Flint, L. G. Grimmett, E. R. Carling and Stanford Cade, *Brit. med. J.*, i/1934, 653.

Protection.—The increasing use of Radium Beam Therapy has suggested some experiments, leading to the conclusion that nurses and attendants should not remain for any appreciable time at distances within, say, $1\frac{1}{2}$ metres behind the bomb, $2\frac{1}{2}$ metres from the side of it, or $4\frac{1}{2}$ metres in front of it in the direct beam.—*Brit. med. J.*, ii/1934, 952.

Radiation (radium) treatment of cancer of the mouth and pharynx. The greatest advance lies in the development of mass radiation—the immediate results obtained surpass anything that has so far been obtained in radium therapy. It has reached equality of status with surgical excision as regards operable cases and in inoperable cases it is the only available method of treatment. A statistical survey of results and details of mass radiation treatment.—Stanford Cade, *Lancet*, ii/1933, 8.

RADON, or radium emanation, is also used in the treatment of malignant disease. Its therapeutic indications and the radiations emitted are identical with those of radium salts, but in calculating dosage, allowance has to be made for the fact that the intensity of radiation is not constant, but is continuously decreasing, falling to half its value in 3.85 days. In the complete destruction of a millicurie of radon, γ rays equivalent to 132 mg.-hrs. are emitted. The γ rays from a radium needle remain constant during a treatment, whereas the activity of the radon decreases exponentially with time. Their biological effects are not therefore necessarily equal. The emanation is filled into small gold or platinum containers; these are implanted in the tumour and allowed to remain in position for a calculated period of time. The containers, or “seeds,” have a thread attached, and frequently this is fixed in position with the aid of a solution of mastic in benzene.

The seeds contain 1.5 millicuries of radon at the time of implanting, giving 200 millicurie-hours’ radiation if left for 14 days. The platinum screen allows about 90% of the gamma rays to

pass through, with less than 5% of beta rays. A trocar with special cannula is used for implanting the seeds, which are implanted about 2 cm. apart. While customary to remove seeds when period of activity is over, no ill-effects have been noted where seeds have been left permanently in the tissues. Encouraging results with tumours which are difficult to treat by other methods. The initial response is more rapid than with other forms of radium therapy. The local reaction is brisk in some cases.—P. Gosse and F. E. Chester-Williams, *Lancet*, ii/1928, 32.

CARCINOMA OF THE BREAST. Radon seeds are implanted into the tissue beneath the breast in such a manner that the whole of the breast and its lymphatic drainage is exposed to a uniform radiation sufficient to destroy carcinoma cells whether in the tumour, the breast, or the lymphatics. About 100 seeds are introduced, each containing 0.5 to 1 millicurie, and the bulk of the seeds will lie in the fascia covering the pectoralis major. By inserting the rows of seeds at right angles a kind of grid of seeds is formed beneath the tumour. Irradiation by means of seeds presents immense advantages in advanced cases and elderly patients, giving results at least as good as those from amputation, with less inconvenience and no disfigurement. In early cases it may be used with considerable prospect of success. To avoid skin reaction and ulceration the whole of the breast and surrounding region should be covered with zinc and castor oil ointment, removed and replaced daily.—H. S. Souttar, *Brit. med. J.*, i/1933, 81. In hopelessly inoperable cases radon seeds are preferable to any other form of treatment.—J. K. Harper, *ibid.*, 936.

CARCINOMA OF THE ŒSOPHAGUS treated by radon seeds. Of 16 cases treated 1 was alive and well after 3 years, 2 lived for more than a year, 11 obtained considerable temporary relief, 2 were not relieved, and 3 were able to remove gastrostomy tube. (Successful operative extirpation is a virtual impossibility and operative mortality is in the region of 100%.)—T. B. Jobson and G. L. Steele, *Brit. med. J.*, i/1934, 233.

CARCINOMA OF THE UTERINE CERVIX. Advanced cases once doomed to die unaided by anything more than palliation, can now be successfully treated by implantation of screened radon seeds. **CARCINOMA OF THE BLADDER AND PROSTATE** also successfully treated.—Joseph Muir, *Lancet*, ii/1929, 7.

Some patients treated with X-rays and radium with no results recover after a single application of radon. Results better where no previous treatment had been applied and where the intratumoural method of treatment is applicable. The introduction of needles is advisable only where the tumour is sufficiently large and is not closely adjacent to the bone; best results in cancer of the tongue, lip, penis, and other similar organs, but the application of masks with radon gave favourable results in other parts. The average dose for superficial application or filtration through 2 mm. of lead is 1 to 1.5 mcd. (millicuries detruites decomposed radon) over 1 sq. cm. of surface, decreasing this for large areas (100 sq. cm. or more). The radon is usually left for 7 to 10 days.—M. I. Newman and F. S. Grossmann, *Brit. J. Radiol. N.S.*, June 1928, 187; July 1928, 24.

MALIGNANT DISEASE OF THE UPPER AIR AND FOOD PASSAGES. Surgical removal of the growth should be undertaken when practicable. The lymphatic nodes should be removed, and the lymphatic vessels between the growth and the infected nodes irradiated, preferably from within. Where possible, the growth to be irradiated should be exposed. The introduction of a number of seeds of emanation better than implantation of screened tubes. As the periphery of the growth is reached the emanation dose may be reduced. 10, 20 or even more seeds are buried. The seeds, from 3 to 6 mm. in length and 1 to 2 mm. in thickness, containing a dose of 0.5 to 1 mc. of emanation, are implanted parallel 1 cm. apart and become encapsuled or slough out.—Sir W. Milligan, *Brit. med. J.*, ii/1926, 825.

RELATIVE VALUES OF SURGERY AND RADIATION

In a discussion at the International Conference on Cancer, London, July 1928, G. REGAUD (Radium Institute, Paris), said that radio-sensitivity of cancer was extremely variable. Of the two different species of cancer of the cervix uteri, epidermoid (a stratified pavement epithelioma, showing structural

the morphological changes or manner of growth peculiar to the epidermis) and glandular, cures by selective radiotherapy had been obtained only in the former, due apparently to the activity and rhythm of division on the one side, and the secretory function on the other. In addition, many factors independent of radio-sensitivity influenced the results of radiotherapy, e.g., extent of primary cancer, its distant spread, its accessibility, and the radio-resistance of the intervening tissues and organs. Ray action could be used on a small neoplasm where it was out of the question in a more extensive one.

Cancer of the cervix uteri. M. DONALDSON (St. Bart's.) gave the following grounds for definitely deciding in favour of radiation as against hysterectomy—(1) the negligible mortality with radiation, (2) statistics of survival-rate in no way inferior, (3) with improved technique, more patients will seek early advice, with consequent improved results, (4) it will bring into general treatment radiotherapy in incurable cases, (5) it will encourage the younger gynaecologists to adopt a method of treatment which they will be able to carry out more successfully than the difficult Wertheim's operation. W. P. HEALY (New York): The most important determining factors in prognosis were the clinical stage of the disease and the radio-sensitivity of the tumour, and, when surgery was employed, early diagnosis and the degree of malignancy. COMYNS BERKELEY (London), gave figures relating to the radical operation. He considered that if the glands were carcinomatous the immediate operative mortality was raised from 12% to 20.6%. VICTOR BONNEY (London) thought a five-year survival period not enough—ten years should be taken before absolute cure was claimed.

Cancer of the rectum. Sir C. GORDON-WATSON described his method of approach by open operation through the perineum, with radium barrage per vaginam and radium in bulk in the lumen of the rectum, employing radium salt in platinum needles. J. P. LOCKHART-MUMMERY: When operation is performed under the most favourable conditions the mortality is about 3.5% and cures, on a five-year basis, are 50%. The best method of treatment is operation; the prospects of cure are good, and where operation is possible the substitution of radiation is not justified.

Cancer of the breast. Prof. BURTON LEE (Cornell University): Irradiation in conjunction with conservative surgery had justified itself. Other speakers were in agreement with this view.

Cancer of the buccal cavity. DOUGLAS QUICK (New York): Radium preferable to X-rays. Filtered radon "seeds" employed with good results. Applicators within the mouth were of no value. STANFORD CADE (London): Surgical treatment had given results so indifferent that those obtained by radium appeared brilliant. In an operable growth the choice should be local excision with the diathermy knife and subsequent irradiation of the scar.

Medical Research Council's Report on the Medical Uses of Radium (1933.) Data collected from the research centres for the years 1930 to 1933, inclusive, show that a total of 7,955 patients suffering from malignant disease have been treated. Of these 29% were treated by surgery alone and 43% by radium alone. In 1933 the figures were respectively, 22.8% and 50.9%.

CANCER OF THE BREAST. Results obtained at St. Bartholomew's indicate that the five-year survival rate is about the same for the two branches of treatment, being about 40% in each case; it is now decided there to combine interstitial radiation with surgery, the breast and glands being excised after radiation, and to compare the five-year survival rates with those of operation and radium respectively.

CANCER OF THE CERVIX. The Marie Curie Hospital reports a steady improvement in the ratio of early cases. Treatment is by intercavitary radium alone.

CANCER OF THE BUCCAL CAVITY. Primary lingual growths are dealt with at most radium clinics by radium, either interstitial or by means of larger units externally; with regard to glands there seems an even balance of opinion and practice between surgical removal and irradiation. A slight improvement in oesophageal cases has followed the distribution of large doses of radon seeds (8 instead of 4 of 3 mc. each) throughout the length of the growth.—*Brit. med. J.*, ii/1934, 821.

CANCER OF THE TONGUE. The present position is that excision of the tongue has given place to radiation. A table compiled from the records of ten institutions during 1931 (none of which specialised in radium treatment) shows that fewer

cases were treated by surgery alone than by radium alone, while radiation treatment of some kind entered into the therapeutic measures adopted in 67·5% of all cases.—“The Medical Uses of Radium,” *Spec. Rep. Ser. med. Res. Council Lond.*, No. 174, 1932; *Brit. med. J.*, ii/1932, 893.

Five-year results (Middlesex Hosp.) equal or excel those of operation, but combination of radiation with operation may double the percentage of five-year surgical cures.—J. H. Douglas-Webster, *Brit. med. J.*, ii/1932, 47.

ELECTROTHERAPY

THE USE OF GALVANIC, FARADIC AND SINUSOIDAL CURRENTS FOR THE TREATMENT OF DISEASE

For the diffusion of the knowledge of the uses and capabilities of electricity as applied to medicine, we have to thank the late Dr. Lewis Jones, Medical Officer in the Electrical Department of St. Bartholomew's Hospital, London. Owing to his researches we are now able to realise that the physiological and therapeutic effects of electricity are the consequence of certain chemical and physical changes, either ionic or thermal in character, that it brings about in the body tissues. Although there are still many gaps in our exact knowledge of the links in the chain of events which connect the application of electricity and its therapeutic results, we know enough to justify us in believing that it is rational and, if properly applied, a very valuable, method of treatment.

If we immerse two copper wires leading from the poles of a galvanic battery in a solution of either sodium chloride, sodium hydroxide or hydrochloric acid, without the wires touching each other, the ions, which had previously been moving about in no particular direction, now, under the influence of the electromotive force (E.M.F.) of the battery, migrate in an orderly manner in definite directions—those ions with positive charge (kations) migrate away from the positive pole (anode) and make their way towards the negative pole (kathode)—those with negative charges (anions) migrate towards the positive pole of the battery (anode).

When the positively charged kations and the negatively charged anions reach the negative and positive poles respectively, they lose their electric charges and become free unelectrified atoms and chemical caustics are formed.

The ions in the tissue fluids, in which the most numerous ions are those of chlorine and sodium, can likewise be made to migrate and form new chemical compounds at the electrodes. The chemical compounds are alkaline at the negative electrode, and acidic at the positive electrode, if it be made of platinum, but neutral if the positive electrode be made of zinc or copper.

Sodium hydroxide and hydroxyl ions, hydrochloric acid and hydrogen ions, zinc chloride and zinc ions, and copper chloride and copper ions are all caustics. The use of the galvanic current

for the production of caustics in abnormal or unnecessary tissue in order to destroy it is a form of galvanic treatment known as Electrolysis, Surgical Ionisation or Electro-chemical Cauterisation. The active electrodes used are narrow metal rods varying in width from 0·2 mm. to 1 or 2 mm. They are inserted into tissue or introduced into channels.

Electrical currents used in the treatment of disease are the following:—

1. Galvanic.
2. Faradic (a) Primary.
(b) Secondary.
3. Sinusoidal alternating (a) Quick.
(b) Slow.
4. Combined currents { (a) Galvano-faradic.
(b) Galvano-sinusoidal.
(c) Galvanic } in combination
(d) Faradic } with diathermic
(e) Sinusoidal } current.
5. High frequency { (a) from d'Arsonval generator.
(b) from diathermic current generators.
(long wave) (short wave)
6. Currents derived from static electrical machines.

Galvanic Current

Galvanism or "Iontophoresis Without Therapeutic Ions." Galvanism has been practised since the middle of last century and employed for relieving pain and aiding resolution of inflammation after injury, but we do not know how it brings about the therapeutic results, which it undoubtedly does, in some pathological conditions. The principal diseases and morbid conditions suitable for treatment by galvanism are as follows:—

In *inflammation due to trauma*, the current aids in the absorption of inflammatory products. It thus usually causes rapid relief of pain and swelling in bruises and sprains, also in fractures and dislocations (after reduction). If the cause of the inflammation has not disappeared or ceased to act before the current is used, the relief, if any, is transitory.

In *osteoarthritis*, the galvanic current occasionally procures temporary relief, the best results being obtained in cases following trauma. In infective arthritis, it may assist in restoring mobility to the joints after the primary focal infection has been removed. In all cases of arthritis, except perhaps those which are definitely due to traumatism alone, there is some fundamental cause or some focus of infection. Until these conditions have been effectually attended to, the results of any local treatment are usually disappointing.

The current is often effective as a pain-killer in cases of *neuritis and fibrositis* after medicinal and other treatment has failed. In cases of *indolent ulcer and indolent wounds*, the process of repair is stimulated or accelerated by the galvanic current (making the kathode the active electrode).

Erythema pernio (chilblain) responds rapidly to this current (the surging sinusoidal or surging faradic currents are equally effective, and if supplemented by local and general diathermy and appropriate internal medication, the effect is more lasting).

The endurance of voluntary muscular effort is very greatly increased by the passage of a galvanic current, which also mitigates or abolishes the fatigue felt

during or after the effort. It has been suggested (Cumberbatch) that the "**refreshing action**" of the current is due to the migration of sarcolactic acid ions from the muscle fibres into the blood vessels or lymphatics.

The refreshing action possibly accounts for the beneficial results of galvanism in the treatment of **Raynaud's disease**. The frequency and severity of the attacks can usually be diminished by passing the current between the hands (or feet) immersed in water (anode) and the cervical (or lumbar) enlargement of the spinal cord (kathode).

It is possible that the relief of mental fatigue (psychasthenia) after the passage of the current through the head (cerebral galvanism), and the feeling of well-being after the current has been passed through the spinal cord, in cases of neuro-muscular neurasthenia, may be due to the removal of fatigue products by a process analogous to that which has been suggested in the case of tired muscles.

Some cases of **progressive muscular atrophy** are benefited by the application of the galvanic current to the spine. The same treatment often relieves the crises, pains, and unsteadiness of gait in **locomotor ataxy**.

Method of Treatment. The electrodes, except when used for special regions such as the middle ear, rectum, colon, uterus, etc., are metal plates made of thin sheet lead or tin alloy padded with several layers of lint or bath-towel material soaked in 1% to 2% solution of common salt at a temperature of about 100°F.

The padded electrodes are applied, one to the part requiring treatment (this is called the *active* electrode); the other (*indifferent* or *inactive* electrode) is applied to a distant part of the body away from the part requiring treatment. Before applying the padded electrodes, the skin to which they are to be applied should be washed with soap and warm water, and then well rinsed with warm water so as to remove the soap. Any cut, scratch, pimple, etc., however small, should be covered by thin sheet rubber adhesive plaster or a drop of collodion.

The pads may consist of 16 layers of lint or 8 layers of bath-towel material of medium thickness, so that after they have been well soaked in the solution of salt (which constitutes the electrolyte) and wrung out they are not less than $\frac{1}{2}$ inch in thickness. During the passage of the current, the chemical caustics will be formed where the metal plate makes contact with the electrolyte, but if the pads are sufficiently thick, the metal plates are at a sufficient distance from the skin to prevent the chemical caustics from reaching the epidermis and causing so-called "burns." The sodium ions at the positive pole and the chlorine ions at the negative pole will conduct the current between the metal plates and the skin and thus complete the circuit, and the galvanic current will pass through the body.

When the padded electrodes have been accurately applied and bandaged on and the circuit is complete, the current is started from zero and very gradually increased, several minutes being expended before reaching the desired maximum. (During the application, the sensations felt at the skin surfaces should be *evenly diffused*. If the patient complains of a *point* of special pain, or if the milliamperemeter needle is observed to move forwards after a period of rest, apart from any movement of the current regulator, it may signify a breaking down of the skin

resistance, and possible injury to the epidermis. Whenever these signs are noticed, the current should be reduced to zero, the pads removed and the skin examined. If the skin has been damaged, a dark grey area will be seen in place of the normal erythema.) It is allowed to flow at this strength for the appropriate time and then it is very gradually reduced to zero.

Current density, or the density of the current in the skin, is the number of milliamperes passing per square inch or square centimeter of electrode in contact with the skin.

Patients can rarely tolerate more than one or two milliamperes to the square inch to begin with, and during the first treatment it is not wise to exceed this amount. Patients have idiosyncrasies to electricity as well as to drugs. In different subjects the sensitive-ness of the skin, even if the latter is apparently normal, varies exceedingly. Some subjects are liable to develop urticaria with a current density that produces no harmful effects in others. If, however, the skin develops urticaria, the current should not be passed again until the eruption has disappeared.

"If a part of the central nervous system (brain or spinal cord) or an organ of special sense (such as the eye, internal ear or semicircular canals) lies on the path of the current, the latter cannot attain as high a density as the skin without causing disagreeable sensation on the part of the patient."—Cumberbatch.

A *visible physiological change* is a patch of erythema which can be observed in the skin where it was covered by the electrodes. These patches of erythema are due to vasodilatation, not merely in the skin but according to certain evidence, in the deeper parts as well. The production of this "galvanic erythema" is the probable explanation of the beneficial results of galvanism when applied to a region which is the seat of passive congestion or of inflammation which has failed to resolve.

Kataphoresis or "**electric osmosis**" is the passage of water from the anode to the kathode during the flow of the current. Whether kataphoresis takes place in such a complex conductor as the body to any appreciable therapeutic extent is uncertain, although some authorities ascribe the good results obtained by "chlorine ionisation" of an ulcer, as being due to kataphoresis and not to the chlorine ions.

The phenomenon named **anelectrotonus** (the lowering or even temporary abolition of excitability and conductivity in muscle or nerve at the anode) is sometimes cited as an explanation of relief of pain which can be procured by means of the current.

Iontophoresis with Introduction of Therapeutic Ions or "Ionisation," "Medical Ionisation," "Kataphoresis."

This is a form of treatment in which the galvanic current is used for the purpose of making ions possessing therapeutic properties migrate into the body.

The term *ionisation* as applied to liquids, strictly means or implies the disassociation of a substance into ions without the

application of any external force, as is the case when a salt is dissolved in water. Inasmuch as the galvanic current in the body consists of streams of migrating ions, the term "*iontophoresis*" (signifying the *conveyance of ions*) is more applicable. The term *kataphoresis* as applied to this method of treatment is impressive but misleading.

The publication in 1900 by Professor Stephane Leduc of the first of a series of papers on the subject, may be said to mark the dawn of the ionisation era. In these papers, Leduc explained the principles of the subject, and indicated the proper technique and the directions along which success might be pursued.

Dr. Turrell, who has apparently no belief in the efficacy of the specific ions (with the exception of those of zinc and copper), in summarising the *argument against the theory of ionic medication*, says:—

- (1) That the function of the solution of salts or "drugs" with which the pads are moistened is to supply the ions necessary for the transmission of the current through mucous membranes or the superficial layers of the skin in an area which is normally very deficient in ions.
- (2) That the current is conveyed through the body by the tissue ions, chiefly in view of their relative fastness, by the hydrogen kations and the hydroxy anions.
- (3) That while a salt is in an ionic state, its chemical affinity is temporarily inhibited by its electrical charge, therefore as an ion it can have no therapeutic action.
- (4) That the very low velocity of the ions employed in medical treatment of this character, and the very low potential at which they are applied entirely preclude the deep penetration claimed for them during the brief period allotted to an electric treatment.
- (5) That, according to Sir Oliver Lodge, "At a change of liquid another set of atoms continues the convection and nothing very particular need be noticed at the junction."
- (6) That such drugs as sodium salicylate, commonly employed, need to be present in the tissues in considerable quantities in order to exercise their therapeutic effect, and it is difficult to conceive that such drugs in the infinitesimal quantities which could possibly be introduced by ionic medication, could have any beneficial action.
- (7) That many workers of extensive experience have failed to detect any difference in these results provided the current is administered at a similar intensity and for a similar length of time, whatever salts or drugs are employed to moisten the pads.
- (8) That very careful experiments conducted both in this country and in France by experienced electro-therapists in collaboration with skilled chemists, have failed to detect the presence of the drug, after its attempted introduction by electrical means, deeper than the superficial layers of the skin.

The late Dr. Lewis Jones, to whom we owe the introduction of ionic therapy into England, wrote as follows in the preface to his monograph entitled *Ionic Medication*:—

"The evidence which has thus (by a record of actual clinical results) been brought together, offers the best of proof that the practice of *ionic medication is a real addition to our means of healing disease*. In view of the facts adduced, we need not too greatly concern ourselves with academic discussions as to whether there is any effective penetration of ions or not. At least we may say that the procedures described have been followed by results of value."

“At the same time we may learn from this collection of cases that the best results have been gained in superficial affections, and we must not be too confident of securing brilliant effects in the more deep-seated affections.”

Cumberbatch (*Essentials of Medical Electricity*) says: “In some diseases the therapeutic effects are certainly due to the ions that are introduced, although the current, apart from the ions that have gained entry, may assist in the production of these effects. In other diseases it is uncertain whether the special ions that are introduced play any part. In these, the therapeutic effects are to be attributed mainly, and some writers would say entirely, to the action of the current itself—that is, to the migration of the tissue ions.”

As time has gone on it has been shown that fewer and fewer of the successful results in various affections are really due to the therapeutic ions that were introduced. In days gone by, a great variety of therapeutic ions were employed. Nowadays the most commonly used ions are those of zinc and copper. Mercury magnesium, salicylic and iodine ions are occasionally employed. *Many authorities would restrict the list to zinc and copper ions.*

The lithium, iodide and salicylate ions have been made to pass through the skin (if applied at the proper poles) and have been detected in the urine and saliva. Leduc, experimenting upon rabbits with shaved sides, has not only proved the penetration of cyanogen and strychnine ions, but has shown that the former (CN) only enters from the kathode and the latter from the anode. In both cases the animals died. The entrance of these poisonous substances is not by diffusion, because control animals with pads soaked in solutions of potassium cyanide or strychnine hydrochloride in contact with the shaven skin, and kept there indefinitely, were not affected if the current was not made to flow. Furthermore, they were not affected if the current was made to flow and the pad electrodes were connected to the wrong poles of the source of current. Again, if a pad soaked in a 1% or 2% solution of zinc sulphate is applied to the granulations at the base and edges of an ulcer and kept there for 10 minutes, it produces no result that is visible to the eye. If, however, a metallic electrode connected to the positive pole of a source of galvanic current be placed over the pad (the indifferent electrode being applied elsewhere) and the latter allowed to flow for 10 minutes, the granulation tissue acquires a pearly-white colour not only on the surface but in the deeper parts. This white colour is due to the formation of a compound of zinc and albumen. The zinc ions have entered, and many have combined with the tissue proteins.

The *regions which can be treated by introduction of therapeutic ions* are as follows:—any region of the skin when inflamed, with or without ulceration, also fistulæ and artificial sinuses which open on to it; any mucous membranes which are within reach of the active electrode, viz., those which line the following regions: nasal cavities, frontal sinus, maxillary antrum, eyelids, cornea, sclerotic, tongue, mouth, Eustachian tubes, middle ear (if the membrana tympani is perforated), anal canal, rectum, colon (as far as the splenic flexure), vagina, canal of the cervix and body of the uterus.

The electrodes when applied to the surface of the body, consist of metal plates and absorbent pads like those described in the treatment termed galvanism or “iontophoresis without the introduction of therapeutic ions.” The “active” pads are soaked in the solutions containing the ions to be introduced. Electrodes of this kind may be applied to ulcers of the skin if not too small, the metal plates and pads being cut to suitable sizes. If the ulcer is only $\frac{1}{2}$ inch or less in width, a small pad of cotton wool soaked in the solution is placed over it, and then a zinc rod is applied to the pad. For the treatment of still smaller ulcers, cotton wool wrapped round the end of a zinc rod and soaked in the solution may be used. In the treatment of an intractable form of corneal ulcer known as Mooren’s ulcer, a bare zinc rod is used. Bare rods of zinc or copper are also used in the

treatment of narrow channels such as the cervix uteri and artificial sinuses of small calibre. (When the current flows, the metal, if connected to the positive pole, slowly passes into solution, so that ions are formed. These ions then migrate into the tissues.) In the treatment of internal parts such as the rectum, colon, maxillary antrum, middle ear, etc., the cavity is first filled with the solution, which is then connected to the source of galvanic current by a special metallic electrode.

Properties and Sources of Various Ions. The old mnemonic used was Metals and Alkaloids are Positive (M.A.P.). Of recent years the more academic mnemonic, Hydrogen Alkaloids and Metals are Positive (H.A.M.P.) has been adopted. All other ions are negative.

When they are prepared for use, the strength of the solution should as a rule be made 1%.

If *iodine* is dissolved in potassium iodide the solution for use should contain 0.5% of each. The strength of *adrenaline* should be 1 in 5000.

The ions of *zinc, copper, silver and mercury* all possess germicidal and cauterising properties. They do not penetrate deeply owing to the readiness with which they enter into combination with the tissue ions and form more or less insoluble salts. When these specific ions pass into the cells they destroy the protoplasm and enter into combination with the proteins formed by its decomposition. In this way, there are formed the insoluble albuminates of these four metals. It is probable that zinc ions penetrate the more deeply, therefore they are used in preference to the others in the treatment of ulcers and sinuses.

Ions with Positive Charges.

Zinc ions are most conveniently derived from a solution of zinc sulphate. They are employed in the treatment of ulcers, sinuses and infected conditions of mucous membranes. The zinc albuminate is an ideal dressing, being tenacious and sterile. It remains in position for 7 to 10 days. During this time the underlying tissues cannot be re-infected from without. Within this layer, bacteria are killed and capillaries are sealed.

Copper ions (derived from a solution of copper sulphate) possess the same therapeutic properties as those of zinc.

Mercury ions (derived from a solution of mercuric chloride) possess the same properties as zinc, copper and silver ions. They are antiseptic, and may be used for the treatment of syphilitic ulcers.

Silver ions (derived from a solution of silver nitrate) are not frequently employed. They form very insoluble salts when they meet tissue ions, including the chlorine ions, and therefore the ions of this metal migrate for a much shorter distance than those of zinc and copper.

Magnesium ions (derived from a solution of magnesium sulphate) do not possess cauterising power. They are used in the treatment of small multiple flat warts which occasionally occur on the hands or face. If this method is going to be successful only one or two applications are necessary.

Lithium ions (best derived from a solution of lithium chloride) have been used for the treatment of gouty arthritis. The passage of the galvanic current without the lithium produces equally good results, especially when combined with salicylic ions.

Quinine ions (derived from a solution of quinine hydrochloride) have been used in the treatment of neuralgia and painful neuritis. Although they are credited with analgesic properties, they are apt to cause marked skin irritation (e.g. when applied to the face in cases of trigeminal neuralgia) so that sufficiently massive currents cannot be comfortably borne.

Cocaine ions (derived from a 10% solution of cocaine hydrochloride) produce superficial anæsthesia. These are usually combined with *adrenaline ions*, in order to procure vasoconstriction at the same time as local anæsthesia. The results are unreliable—a local injection of procaine and adrenaline is preferable.

Histamine ions (derived from a solution of histamine hydrochloride) have been recently claimed to be efficacious in the treatment of non-infective affections of the muscles and joints. Katexon Foil is used. This consists of sheets of filter paper saturated with a solution of histamine hydrochloride and covered with a thin coating of aluminium which acts as a conductor of the current. Before use, the Katexon Foil must be soaked in water.

Histamine ointment gives better results and is more convenient in use than solution, the part affected being smeared with the ointment and a lint pad, wrung out of saline, placed over the part and connected to the anode of the apparatus. Patient given the maximum milliamperage which can be tolerated, frequently up to 100 or 150 ma., the current being raised to maximum as rapidly as compatible with patient's comfort and maintained as high as patient will allow to end of sitting. The tolerance of a patient both as to time and milliamperage varies greatly from day to day. There is immediate tingling and intense itching at site of anodal pad, with feeling of local warmth, and patient must be told how to distinguish between this and burning due to concentration of current; also to complain if limb begins to throb, face flushes or if there is pain in the head. To avoid bad headache, current must be cut off at first suspicion of flushing, and reduced if throbbing or excessive heat occurs. The relief of pain, either complete or partial, may last a few hours, a few days or permanently. Undesirable results, indicating immediate cessation of sitting, include headache, tachycardia, constriction of chest, with breathlessness, burning, and faintness.

Treatment may be given daily. Has no place in the treatment of infective arthritis, acute rheumatoid arthritis or where there is marked failure of compensation in the heart, but of special value in fibrositis and neuritis, which it is possible to cure. Massage with the ointment also satisfactory but less so than ionisation.—F. S. Mackenna, *Lancet*, i./1934, 1228.

Ions with Negative Charges.

Chlorine ions (derived from a solution of common salt) are used for softening superficial scars which are the result of trauma or burns, and for loosening superficial adhesions. The best results are produced by a combination of radiant heat or diathermy, "chlorine ionisation," and massage and movements in direct sequence and on the same day. If the scar be painful, salicylic ions are preferable to chlorine ions. The modern belief is that chlorine ions have no direct "sclerolytic" action and that the beneficial results are probably due to kataphoresis.

Iodine ions (derived from a solution of potassium iodide) have also been used for softening scar tissue, but it is doubtful whether they exert any specific action in the process. They have antiseptic properties and may therefore be introduced into syphilitic ulcers. The addition of free iodine to the solution of potassium iodide increases their germicidal action, and makes them very successful in the treatment of chronic non-specific infected ulcers and sinuses.

Salicylic ions (derived from a solution of sodium salicylate) possess weak germicidal powers and are well borne by the tissues.

They have been found very efficacious in relieving both superficial and deep conditions when attended with pain—e.g. painful scar tissue and ulcers, and trigeminal neuralgia.

Diseases and Morbid Conditions for which "ionisation" is a valuable form of treatment often after other measures have proved unsuccessful

CHRONIC INFECTIVE PROCTITIS. Zinc ionisation generally successful—using a special electrode.

ULCERATIVE COLITIS. J. Curtis Webb (*Lancet*, ii/1905, 1361) advocated the use of silver ions, using a special electrode and technique. Zinc ions were afterwards used instead of silver ions and Julius Burnford (*Brit. med. J.* ii/1930, 640) described the results of the treatment in 28 cases.

MUCOUS COLITIS. Salicylic ions may be used (pelvic diathermy applied by the rectal route is often successful).

CERVICITIS. Very successful. Begin treatment by placing a zinc electrode in the canal of the cervix, make it the *kathode*. This causes a migration of hydroxy ions into the cervix, where they destroy organisms and convert the cells into alkaline albumen. There is also an increase of the secretion from the cervical glands, thus establishing efficient drainage. It is of special value when the discharge is slow, thick and adherent. When the discharge is thinner and more copious the active electrode should be connected to the positive pole of the source of current; zinc ions are thus introduced and zinc albumate is formed. (For full details consult E. P. Cumberbatch's *Essentials of Medical Electricity*.)

CHRONIC SUPPURATIVE OTITIS MEDIA (if there is an opening in the membrane of the tympani). If there is no caries of the bone, no papilloma or cholesteatoma, two or three treatments by zinc ionisation, using 0.5% solution of zinc sulphate, are usually effective. The solution is introduced by way of a special electrode recommended by Friel ("Zinc Ionisation and Zinc Electrolysis in Treatment of Chronic Otorrhea," *Trans. Roy. Soc. Med., Otol. Sect.*, 1921), or by a special electrode designed by W. Cloughton Douglass ("An improved method for the treatment of otitis media by ionisation," *Brit. J. Bio-phys.*, 1930). A current of 2 to 3 milliamperes is passed for 10 minutes.

CHRONIC RHINITIS of the catarrhal type and cases of spasmodic rhinitis including those of "hay fever," can in some cases be effectively treated by zinc ionisation. Special electrodes are required (see P. Franklin, *Brit. med. J.*, i/1930, 751).

MAXILLARY ANTRUM AND FRONTAL SINUS. Chronic inflammation of the mucous membrane of these parts can occasionally be brought to an end by zinc ionisation. Sometimes salicylic or iodine ions are introduced. Special electrodes and technique.

CORNEAL ULCERS. Use retractor, cocainise eye, instil fluorescein. A tuft of cotton wool soaked in a 1% solution of zinc sulphate is wound round the end of a zinc rod. The free end of the tuft is placed on the ulcer, the rod is connected to the conducting wire leading to the positive pole of the battery. A current of 1 to 1½ milliamperes should be passed for 1 or 2 minutes. If the ulcer does not heal after 10 days a second application should be made. One application is sufficient to effect a cure if the ulcer is small. In treating "Mooren's ulcer," after cocainising and instilling fluorescein, apply a zinc rod, $\frac{1}{16}$ in. diameter with its free end rounded, to the edge of the ulcer. A current of half a milliampere is passed and the rod is moved very slowly along the edge. Each part covered by the zinc rod should receive the current for 15 seconds. After the lapse of 14 days, instil fluorescein and treat again any part which stains.

NON-SPECIFIC ULCERS OF THE SKIN. Zinc ions are generally introduced. The resulting pearly-white zinc albuminate is a tenacious, sterile, protective covering, and until it disappears no further electrical treatment should be given. One treatment is often sufficient. Zinc ions are most useful in cases of infected ulcers; sometimes "varicose" ulcers can be healed by the same method. If the ulcer be inflamed or painful, one or two preliminary treatments by salicylic ions are often effective. Iodine and salicylic ions sometimes succeed when zinc ions fail. When an ulcer is callous, and infection is not the evident cause of its persistence, chlorine ions should be introduced.

SYPHILITIC ULCERS should be treated by the introduction of mercury or iodine ions.

PERFORATING ULCERS may be treated by introducing the negative ions present in a 1% solution of iodine in a solution of potassium iodide of the same strength.

ARTIFICIAL SINUSES. Success can only be expected when the sinus is more or less straight and has no side channels, does not lead to carious bone and does not contain any foreign body (pledgets of paper or cloth are transparent to X-rays.) First cleanse the sinus to prevent any part of its surface from being shielded by pus or débris. It should then be well filled and even distended with the solution, and the electrode in the form of a zinc or copper rod should be so contrived as to be equally close to all parts of the area. At the commencement of the treatment, the more distant part of the sinus should receive most attention, so that it may heal from the bottom.

If zinc ions are used, a zinc rod is made the *anode*; if iodine ions are used, a zinc rod is made the *kathode*. If the sinus is not too narrow, a zinc rod carefully covered with cotton wool soaked in the solution is passed along the channel. If it is too narrow, a bare zinc rod is used.

The Galvanic Current Used for the Removal of Foreign Ions.

C. H. C. Dalton (*Brit. med. J.*, ii/1929, 297) reports a case of footdrop due to arsenical poisoning, which was successfully treated by the galvanic current. The affected muscles were stimulated by interrupted galvanism thrice a week. The affected limb was then placed in a kathodal foot-bath and, in addition, a pad was placed, reaching up the skin of the leg. The unaffected leg was placed in an anodal leg-bath. After 14 days, the skin under the pad was noticed to be scaly. The scales and the fluid wrung from the pad both showed the presence of arsenic by Marsh's test. The patient was first treated on April 10, 1928—on May 30 the condition almost approached the normal. When examined on June 20 the affected muscles had completely recovered, and normal sensation of the skin on the front of the leg was found. The arsenic in such cases is probably in the form of hydrochloride.

A somewhat similar technique is employed in the treatment of workpeople employed in lead factories—the active electrode is kathodal. After each application, lead has been found in the bath water, even when the patient has been out of work for 10 weeks, and was, therefore, unlikely to have any lead dust present on the surface of the skin. A distinct relief of the symptoms of lead-poisoning was observed, in addition to an improvement in the general health of the patients submitted to the treatment, which is not only preventive but curative as well. (Sir Thomas Oliver: *Lead Poisoning from Industrial, Social and Medical Point of View*, 1915.)

When the galvanic current traverses a fluid containing micro-organisms in suspension, the latter migrate towards the anode. It is likely that this movement takes place where the current is directed through infected fluids, and if the organisms can reach the anode they will be destroyed. A method based on this principle is used by Dr. Charles Russ for clearing the urethra of gonococci.

Electro-chemical Cauterisation, Surgical Ionisation or Electrolysis is a form of treatment in which abnormal or unnecessary tissue is destroyed by chemical caustics produced within it by means of the galvanic current. Caustics such as sodium hydroxide and hydroxyl ions or hydrochloric acid and hydrogen ions are derived from the sodium and chlorine ions in the tissue fluids. On the other hand, when zinc ions are to be used for cauterising purposes, they are derived usually from the

metal itself, which is placed in contact with the tissue to be destroyed. When the metal, in the form of a zinc needle, is connected to the positive pole of a galvanic battery and the current is made to flow, the metal passes into solution, so that its ions are formed and they migrate into the tissue where zinc albuminate is formed. If the positive electrode is made of platinum or platinum-iridium, the tissue in its vicinity is transformed into acid albumen. At the kathode, whatever metal the electrode is made of, hydroxyl ions and sodium hydroxide are formed, and the tissue in the vicinity of the needle is transformed into alkali-albumen.

The details of this **method of treatment** differ according to the tissue which has to be treated. The active electrodes are in the form of needles, varying in width from 0·2 mm. to 1 or 2 mm. Their ends are rounded if they are to be introduced into channels, or pointed if they have to be inserted into tissue. The finer electrodes are best made of an alloy of platinum and iridium. Thicker electrodes are made of hardened zinc. The electrodes are attached to suitable holders made of ebonite or fibre, except in the case of multiple-needle monopolar electrodes, in which each needle is soldered to the bare end of a short length of insulated wire. The other end of each wire is soldered to a common terminal and this terminal is connected to *one* pole of the battery. They may be monopolar, multiple-needle monopolar, bipolar or multiple-needle bipolar.

A monopolar (or unipolar) electrode may consist of one, two or more needles. When it is used, the circuit must be completed by means of an indifferent electrode—a padded metal plate like that already described. When the electrode is bipolar or multiple-needle bipolar, all the electrodes are active.

The *advantage of cauterising tissue by the electro-chemical method* is the fact that the method is under exact control of the operator, so that the current can produce the amount of caustic desired precisely in the situation desired with little subsequent reaction and the formation of soft non-contracting scars. The limitation of the method is the fact that only a small amount of tissue can be destroyed at each application or insertion of the electrode. More tissue can be destroyed if inserted successively into adjoining regions, but this process is slow and tedious both to the patient and to the operator. If the electrode consists of a group of needles, the tissue can be cauterised at a quicker rate.

Therapeutic Field. Electro-chemical cauterisation is an efficient form of treatment for certain maladies and disfigurements of the skin and mucous membranes, such as hypertrichosis, cavernous nævi, stellate veins, telangiectases, newly grown venules in the skin, nævi composed of separated vessels and pedunculated warts. It is also efficient in the treatment of cases of chronic peripheral neuritis, such as sciatica and tracheal neuritis.

HYPERTRICHOSIS (superfluous hairs). The procedure requires much practice, skill and patience. Thick and dark hairs, not too close together, are easiest to remove. (Fine, downy hair should not be thus treated.) When a large surface has to be done, it is better to remove hairs from every part and not from one spot, otherwise a troublesome ulcer would probably result. About twenty is the largest number that can be removed at a single sitting.

CAVERNOUS NÆVI. Use a Lewis Jones' multiple-needle bipolar electrode. Sterilise needles in the flame of a spirit lamp, and then push them into the nœvus at the level of the skin. After current has flowed for half a minute, partially withdraw the needles and push them in again in a different direction. Repeat process if necessary, so that the needles explore all parts of the nœvus, and pass through its blood vessels. Current should not exceed 20 milliamperes for each inch of positive needle inserted, otherwise a slough is apt to be formed. Give special attention to the margin, and supplement if necessary with the galvano-thermo-cautery. At interval of 4 weeks repeat treatment if necessary.

STELLATE VEINS. (Spider nœvi). Insert zinc needle (anode) about $\frac{1}{8}$ in. into central vein ("the body of the spider") from which the others radiate. Current of 1 milliampere for one minute.

TELANGIECTASES AND NÆVI, COMPOSED OF VESSELS THAT ARE SEPARATED FROM EACH OTHER BY INTACT SKIN. Insert zinc needle (anode) to depth of about $\frac{1}{16}$ in. Current of 0.5 to 1 milliampere (according to size of vessels) for 30 seconds. Transfix each vessel at intervals.

"PORT-WINE STAINS" may be treated by zinc needling. Electrode is inserted successively in closely adjacent regions. Current of 1 or 2 milliamperes for 30 seconds. Process so very slow that except for small nœvi, electro-dessication or radium is preferable.

WARTS, PEDUNCULATED, SESSILE OR SEMI-SESSILE, and "senile" warts and soft papillomata of the skin. Transfix base with zinc needle (anode). Current of 1 milliampere passed for 1 minute. If base of wart or papilloma is more than 2 or 3 mm. transfixion should be repeated in parallel lines. Flat warts are generally unsuitable for zinc needling—electro-dessication is a better method.

MOLES. Non-pigmented hairy moles should be treated by epilation. If the mole does not disappear, use zinc needling in different directions. Electro-dessication may be supplemented or substituted.

CHRONIC PERIPHERAL NEURITIS: NEURO-FIBROSITIS. TREATMENT BY GALVANIC ACU-PUNCTURE. Bare the region where patient feels the pain, moisten skin with warm saline. Pad electrode is applied to the skin of another part and connected to one of the terminals of a medical induction coil or a source of sinusoidal current. This is the indifferent electrode. (The writer always uses the secondary current from a Lewis Jones' coil.)

The active electrode is a small button electrode about $\frac{3}{16}$ in. in diameter, mounted on the end of a suitable holder. This is connected to the other terminal and is applied to the moistened skin. The current is started and increased until it produces a painless sensation of "pins and needles." The electrode is then moved over the region where the patient refers the pain. If the case is one for which galvanic acu-puncture is suitable, the passage of the electrode will detect a point or points where the current produces *acute* pain. These hypersensitive points are confirmed by repeated exploration from different angles. Slight shifting of the position of the button electrode causes instant disappearance of the acute pain, and the return of the painless sensation of "pins and needles." When confirmed, the "painful faradic points" are marked by a skin pencil with a ring or square round the electrode, and are then subjected to the following treatment:—Tincture of iodine having been applied, a few drops of procaine and adrenaline solution are injected just under the skin at the centre of the spot to be treated. The indifferent electrode is left in position, but is now connected to the *positive* pole of a source of *galvanic* current. The *negative* is connected to the active electrode. The active electrode is a steel needle which is attached to a suitable holder. The needle is insulated except for a distance at its free end (which distance varies according to the probable depth of insertion) by celluloid enamel.* Ordinary sewing or darning needles are quite suitable. The writer, in certain cases, uses a straight blade-shaped Hagedorn needle.

*The insulating enamel is made by dissolving some black celluloid in a mixture of acetone and amyl acetate. The proportions are:—Acetone 47 parts; amyl acetate 47 parts; black celluloid 6 parts. The night before the treatment the needle is dipped into the enamel. The next day the enamel on the electrode will be dry. It can then be scraped away from the free end to the desired extent. The point, before insertion, is momentarily dipped into spirit. After two or three sessions of treatment, the electrode should be held for a moment in the flame of a spirit lamp so as to burn off the remains of the enamel. It can then be dipped in the solution again. The formula of the solution was devised by the late Dr. Muir, of Exeter.

The point of the needle is inserted at the opening made by the syringe needle and should follow the same direction. A galvanic current of one or two milliamperes is passed and the needle electrode is inserted a little more deeply or its point moved about like a probe until the patient feels *acute* pain, often radiating. If the pain be very severe, keep the electrode in exactly the same position and at the same angle, reduce the current to zero and then inject a few minims of procaine and adrenaline solution down the side of the needle electrode as deep as the point of the needle. After 2 minutes' interval, the current is again passed (still keeping the needle electrode in exactly the same position), and, owing to the second injection of the local anæsthetic, the patient can usually tolerate a current of 5 or 6 milliamperes for 5 minutes. The current is then reduced to zero, the needle is withdrawn and a collodion dressing applied. One, two or three hypersensitive spots, according to the sensitiveness of the patient, can be thus treated in succession at the same sitting. If a spot has been exactly located and correctly treated, there is no subsequent pain except perhaps a little "needle soreness," and a repetition of the exploration with the faradic or sinusoidal current 3 or 4 days afterwards, will fail to produce any pain when the testing electrode is moved over the spot which was treated. If the cause of the neuritic pain be still existent, some other tender "faradic points" may subsequently be found. They are treated in the same way. The hyperæsthetic faradic points are found so frequently in the same small areas, that an expert can usually know beforehand where he will find at least some of them.

If the patient be very nervous, it is advisable, when testing for the proper "pins and needles" strength of the faradic current, to move the active electrode over the corresponding region on the *opposite* side. The beneficial effects of this form of treatment are probably due to the cauterising action at the negative pole being exerted, not on a main nerve trunk, but rather on one of its sensory branches along which the pain is referred to the surface.

The galvanic current produces caustic chemicals below the skin in accurately located spots. Galvanic acu-puncture can be used in all cases in which some specialists use injections of absolute alcohol, and is, in the writer's experience, preferable and less painful. This form of treatment should be reserved for *chronic* cases.

The source of galvanic current for iontophoresis and electro-chemical cauterisation may be D.C. main, A.C. main by means of a rectifier, batteries of wet or dry Leclanché cells, accumulators, or dynamo and driving plant (private installation). Those sources should be used, for medical purposes, with the interposition of suitable resistances.

Galvanic Current Used for the Stimulation of Muscle or Nerve.

When treatment by "galvanism" or "iontophoresis" ("ionisation") is being administered, it is necessary to increase and decrease the current with adequate *slowness* in order to avoid causing pain or discomfort to the patient. If a current passed along the body with *constant* strength, it does not stimulate the muscles or *motor* nerves. The *sensory* nerve-endings are, however, stimulated, possibly in consequence of the accumulation of ions in the skin. This stimulation persists during and after the passage of the current, and it may be the cause of the vasodilatation that accompanies it—a feeling of warmth is experienced, and the skin under the electrode acquires an erythema. If the current be *suddenly* increased or *suddenly* decreased, it stimulates both the sensory and motor nerves. If the reduction is less sudden the sensory nerves alone will be stimulated. If the reduction is very gradual, there will be no stimulation. The two factors which determine the stimulating power are the strength attained by the current and the time occupied by the current in rising to its maximum or in falling to zero. When used for the purpose of

stimulation, the galvanic current must be made interrupted, surging or alternating.

Infrequently Interrupted Galvanic Current is obtained when a metronome interrupter is placed between the battery of cells and one of the electrodes. This current is used for producing contraction of muscles which show the reaction of degeneration, the active electrode being placed, in turn, over the motor point of each of the affected muscles. When used for testing the reactions of muscle and nerve, the current is interrupted by means of a make-and-break key which is operated by hand.

Frequently Interrupted Galvanic Current (the Leduc Current). The Leduc interrupter is introduced into the current, which can by this means be interrupted at a much more rapid rate than when the metronome interrupter was used. Although the Leduc current can be used for the purpose of exercising muscles in cases of paralysis, it is practically only used for the treatment of *causalgia*—a very painful affliction which may follow nerve injury.

Surging Galvanic Current. This is a current which rises and falls very slowly between zero and maximum, one second or more being occupied by the rise and fall. The easiest method of obtaining such a current is to move rhythmically the regulating device attached to a “galvanostat” or “ionostat” (instruments connected to the main supply with lamp and water resistances). By moving the regulating handle the operator can make the current surge between zero and the desired maximum. By altering the direction of movement of the handle, the current can also be made to flow in either direction. The surging current is used in the treatment of paralysis in cases where one set of muscles shows the reaction of degeneration and the antagonists show reactions of normal type. The current causes contraction which is limited to muscles showing reaction of degeneration. The paralysed muscles therefore are not stretched. The affected arm or leg can be immersed in water and the current directed along the limb. If an interrupted galvanic current were passed along the immersed limb, the normally reacting muscles would contract with quick twitches and would momentarily stretch the paralysed muscles before they began their sluggish contraction.

Infrequently Alternating Galvanic Current. This current may be obtained from the galvanic current by introducing a *metronomic reverser* into the circuit. This metronome has four mercury cups, two on each side. When the swinging arm is on one side, the current flows in one direction to the patient, and when it is on the other side, the direction of flow is reversed. This alternate anodic and cathodic stimulation is useful in the treatment of muscles showing the reaction of degeneration. Some denervated muscles in a limb give a larger contraction in response to anodal stimulation, others may give a larger contraction in response to kathodal stimulation.

If the alternating galvanic current passes along the limb, all the denervated muscles will receive a more even degree of exercise than they do when the interrupted galvanic (unidirectional) current passes. In the application of the galvanic current, bath electrodes may be used—the water in the bath with the metal or carbon introduced into it constitute the electrode or electrodes. The most commonly used are the leg and arm Schnee baths. Baths are made of porcelain or china, or still better, owing to their lightness, of aluminium lined on the interior by waterproof insulating material. In Raynaud's disease, for instance, the arms or legs are immersed in these baths and connected to the positive pole. The electrode over the spinal cord is made the kathode. In other cases, bath electrodes are convenient for the purpose of completing the circuit when a pad electrode is applied to the part requiring treatment.

Faradic Currents

The faradic current is obtained from an induction coil. The most important property of the faradic current is its power to stimulate the excitable tissues, particularly motor nerves. It is therefore able to produce contraction of voluntary muscle, and it is probable that, in consequence, many or all parts of the body are reflexly stimulated. The faradic current is chiefly used for the treatment of paralysis. Its therapeutic properties in this condition are not due entirely to its power to cause contraction of muscle. If the latter shows the reaction of degeneration, the faradic current is unable to cause it to contract, but it is nevertheless able to hasten recovery and to relieve some of the symptoms which may accompany paralysis, viz. cyanosis, chilblains, trophic sores and other results of defective circulation.

The faradic current is applied in the same way as the galvanic and similar electrodes are used. Since it causes muscles to contract, it is necessary to introduce into the circuit some device which will rhythmically interrupt the current. The muscles will therefore relax during the period when the current is not flowing and fatigue which would be caused by continuous contraction is prevented.

Apart from the prevention of fatigue, currents which are rhythmically interrupted produce better results than those which flow continuously. *This is an important general principle*, and it is true of *all* currents used for the purposes of stimulation, whether the muscles contract or not. Rhythmic interruption of the faradic current can be produced by sliding the secondary coil to and fro along the primary, till the sensation perceived by the patient is as strong as can be borne without discomfort. It is then moved off until no sensation is perceived. About two seconds should be spent in each movement. An alternative method is to include a metronome interrupter in the circuit, and regulate the rate of swing so that the current flows for about two seconds and is interrupted for the same period. Another method of procuring

the necessary periods of rest between those of stimulation is the manual or labile method, to which reference has already been made. The active electrode is a padded metal disc, considerably smaller than the region requiring treatment.

This electrode is rhythmically stroked over the part and lifted at the end of each stroke. The pad of the electrode is soaked in warm saline,—if the padded electrode is occasionally rubbed over a cake of soap the application is more pleasant. This *manual* or *labile* method is suitable for regions such as the face, foot, etc., where the accurate application of electrodes is less easy; it also constitutes a form of massage. Still another method is to make the current *surge*, or wax and wane. After each surge there should be a period of rest before the next surge begins. The duration of each surge should be from one to two seconds, and that of each period of rest should be the same. Some of the types of surging devices most frequently used will be described when discussing *sinusoidal currents*.

As one of the most important uses of the faradic current is to procure contraction of muscle without painful sensation in its passage through the skin (except in some cases of hysteria, drunkenness, and malingering, which require *painful* stimulation), the choice of coil is important. The Lewis Jones sledge coil, the Tripier coil (reintroduced of late years as the Physio coil), and the Spamer coil, are all suitable.

Therapeutic Uses of the Faradic Current. This current is used for practically the same purposes as the quick sinusoidal current. Faradic coils are portable, and are useful in cases where only occasional treatment is required. Where work is heavy and continuous, the sinusoidal current is more suitable.

In treating cases of paralysis or weakness of muscles, the general rule is to use the faradic current if the muscles will contract to it, but if not, to use the galvanic current. *All* forms of electrical stimulation are of use in the treatment of paralytic conditions, if the current be rhythmically interrupted or surged. The general treatment of paralysis will be described later on.

The faradic current may be usefully employed in the treatment of chilblains, constipation, fibrositis with adhesions (in these cases, use the Physio coil with an adjustable interrupter so adjusted as to produce strong muscular contractions about one per second), incontinence of urine (strong applications are necessary), and hysterical aphonia (strong applications are necessary). In the treatment of obesity by faradic current, the muscles are made to contract against resistance (heavy sandbags) and to do work.

The faradic current is also used for procuring strong painful sensation of sensory nerves. This treatment is used for hysteria; also for producing counter-irritation in neuralgia. In such cases, the current from a coil with a long secondary winding must be used, as a high voltage is required. A fine wire brush is used as the active electrode and is stroked over the skin.

Sinusoidal Alternating Currents

In these currents, the rise from zero to maximum and the fall from maximum to zero are gradual. Further, on reaching zero, there is no period of intermission but a second rise to maximum and fall to zero in the opposite direction. The currents are called *sinusoidal* because their graphic record resembles a sine curve.

Quick Sinusoidal Alternating Currents. These currents are devised from (a) A.C. dynamos; (b) D.C. dynamos; or (c) from accumulators. In utilising the current from either of these,

a *rotary converter* is employed. Rotary converters are fitted to the various forms of so-called "Universal Apparatus," such as the Pantostat, Multostat, Polystat, Plurostat, etc., according to the makers. The expression "quick" refers to the duration of each period of flow in one direction before reversal of the current. When the duration is not less than $1/50$ th of a second, the sinusoidal current may be called "quick."

These alternating currents stimulate the excitable tissues, but they cannot cause ions to migrate—they merely cause them to move to and fro. They cannot therefore be used in treatment by "ionisation." They can, however, produce chemical changes at metal electrodes, but in insufficient degree to harm the tissues.

The quick sinusoidal alternating current stimulates muscle and nerve. It causes contraction of muscles which show normal reactions, but it is unable to cause contraction of muscles which show the reaction of degeneration. Nevertheless it possesses therapeutic value in the treatment of paralysis even though it cannot make the muscles contract. Cyanosis and trophic lesions which accompany paralysis of large groups of muscles (as in cases of infantile palsy) diminish or disappear after treatment by this current. Furthermore, in such cases the return of some degree of power to muscles which have long remained powerless, either under expectant treatment or with massage, exercises, etc., is frequently noticed after the sinusoidal current has been utilised for a few weeks.

The quick sinusoidal alternating current (rhythmically varied) is of value in the treatment of *weakness and paralysis of muscles as a result of disease or injury*. In post-influenzal general muscular weakness and mental depression it is very beneficial. Goodall and Wallis found that though the excretion of creatinine is, in general, deficient in the insane, the sinusoidal bath tends to increase it, and that treatment with warm baths alone had very little influence on the creatinine excretion (*J. ment. Sci.*, April, 1910).

The quick sinusoidal current is of considerable value in the treatment of *chronic cases of neuritis*. In acute or sub-acute cases, however, it aggravates the pain. The best results are obtained in cases where diathermy or iontophoresis have diminished the pain but failed to abolish it entirely. As before stated, the current may be used in cases of hyperpiesia, but treatment by general diathermy is usually more reliable.

"Currents which are interrupted or reversed more frequently than once or twice per second should not be passed through the body just as they are, even if the maximum strength they attain is easily borne by the patient. It is obvious that muscles on the path of the current will remain in a state of clonic or tetanic contraction if the periods of rest between the stimuli are too short. Prolonged contraction without rest soon fatigues the muscles, and harmful results follow. Even if there is no actual contraction of muscle, there should be periods of rest between those of stimulation, because biological changes occur in response to electrical excitation of muscle and nerve. Although there is a period of rest between each period of flow in the case of some of the interrupted and alternating currents (e.g., the faradic and Leduc currents) it is far too short to allow the muscles to relax before the next stimulus." (Cumberbatch).

To attain this object, the metronome interrupter may be used. A more satisfactory method is to make the current *surge*. The current is made slowly to wax and wane, gradually rising from zero to maximum and gradually falling from maximum to zero. After each complete surge there should be a period of rest before the next surge begins. The duration of each surge should be from one to two seconds, and that of each period of rest should be the same. For this purpose the apparatus constructed at the suggestion of the late Dr. Lewis Jones

for attachment to the rotary convertor of the Pantostat is very suitable. Tap water in the conical glass is used as the varying vessel resistance. This device is satisfactory for work in private, where one patient is treated at a time. For hospital work it is more customary to use an apparatus for procuring surging sinusoidal alternating current from the main by means of a transformer with a movable secondary coil. The secondary coil suspended by a cable is made to rise and fall over the primary by means of a small electric motor.

Electrodes. The current rhythmically varied should be administered by way of electrodes when local treatment is to be given. These electrodes are similar to those employed for iontophoresis through the skin. They should be of large size, sufficient to cover the whole part requiring treatment. If there is no instrument at hand for producing rhythmic variation, a certain degree can be effected by moving one of the electrodes that convey the current into the body rhythmically over the skin of the area to be treated, and lifting it off at the end of each stroke. In this method the active electrode should not be less than one third of the area over which it is moved.

If the extremities or the entire body are to be treated, electric baths may be used. These are of two kinds—the Schnee bath and the full-length bath. The water in the bath with the metal or carbon introduced into it constitutes the electrode.

The currents for use in the Schnee baths. The current from the main, using a static transformer when the main current is alternating, or a motor generator when it is direct. If there is no main supply at hand, the current from a battery of accumulators may be taken to the motor generator. The sinusoidal current is almost always used when patients are treated in the Schnee baths. The current used in the full-length bath should always be the rhythmically varied sinusoidal. The galvanic current derived from the main should never be used because the risk to the patient from “earth shocks” is too great. As the late Dr. Lewis Jones expressed it, “No method which depends for its safety upon the maintenance of insulation from earth of a bath containing water is good enough to risk.”

References

Electric Ions and their use in Medicine, by Stephane Leduc, translated by R. W. MacKenna, 1908. *Ionic Medication*, 1913, by H. Lewis Jones, and *Medical Electricity*, 7th edn., revised by Bathurst, 1918. *Essentials of Medical Electricity*, 7th edn., 1933, and *Lectures on Medical Electricity*, 1934, by E. P. Cumberbatch. *Principles of Electrotherapy*, 2nd edn., 1929, by W. J. Turrell. *The Present Position with regard to Ionisation*, *Brit. J. Actino-Therap.*, 1930, and *Treatment of Mental Cases by Physical Methods*, *Brit. J. Phys. Med.*, Feb., 1934, by Alastair MacGregor. *Principles of Physiology*, 1918, by W. H. Bayliss.

DIATHERMY

Diathermy is a form of high frequency current in which the oscillations usually vary between $\frac{1}{2}$ and 3 million per second. The circuit consists of a small transformer to raise the mains A.C. supply to about 2000 volts. The rest of the circuit then consists of a condenser, an inductance and a spark gap, the discharges of which initiate the oscillations of current. A valve circuit may be used instead of the spark gap. This type of machine gives a more regular type of oscillation. The patient is usually insulated from the primary circuit by oscillator-resonator coils.

The current is led to the patient by two rubber-covered leads, which should not be more than a few feet long. It may be applied to the patient by lint pads soaked in strong saline solution, or by thin lead or foil plates, closely and evenly applied to the skin. A useful method for the wrists and arms is for the patient to hold a

piece of metal tubing in either hand, the leads being attached to these. A useful handle-bar type consists of an ebonite rod about $\frac{1}{2}$ inch diameter and 6 inches long, and the copper cylinders at either end of the same diameter and about 6 inches long.

The chief effect of these currents when passed through the body is the generation of heat in the path of the current. The amount of heat generated will depend on the current density and the resistance of the part. The greater the product of these two the more heat will be generated. The actual rise of temperature will also depend on how the heat is conducted away, and in the case of most of the internal organs, with their abundant blood supply the rise will not be so great as in less vascular parts. The machine usually has a milliampere meter, but as this does not tell of either the current density or resistance of the part, it is of very limited value, and must not be relied upon. The chief guide is the patient's sensation of pleasant warmth, and it is unsafe to go beyond this or an unpleasant burn may result. These are often comparatively painless, but may take some time to heal. Obviously the treatment should not be given to an anæsthetic area of skin.

Clinically, this property of warming the tissues locally is useful in many conditions, as it stimulates the vascular supply and hence helps the vitality of the tissues. By using large electrodes and large currents the temperature of the body as a whole can be raised (so called "artificial fever"). By using small metal electrodes a great current density can be produced and tissues can be coagulated and burnt.

Cutting Current. By suitable modifications of the circuit a current is produced that disrupts the tissues, and, using small needle or blade-shaped electrodes, the current can cut the tissue. It is possible to adjust the cut very finely indeed, and so is of use in brain surgery. The cut can also be made so that the edges of the wound are coagulated at the same time to a depth of $\frac{1}{2}$ to 2 mm., and thus the lymphatics and small vessels are sealed. This is of use in some cases of cancer.

Short Wave Therapy. Using even higher frequency oscillations (10—100 million per second, giving a wave length of 30—6 metres), heat effects can be obtained by direct inductance, the patient being placed in the condenser field between two electrodes. With this type of oscillation the metal electrodes need not touch the patient, and this makes the application much easier. Bandages or even clothing need not be removed. Of use in conditions where ordinary medical diathermy would be employed, but deep heating may be a little easier, especially where there are irregular surfaces such as the knee or nasal sinus. It may also be used to produce therapeutic fever.

CERVICITIS. By a method devised by C. A. Robinson an infected and inflamed cervix uteri can be heated to the maximum temperature desirable, i.e., 115° F., which will free the cervix of infection by pathogenic organisms. Untreated cervicitis may lead to infective arthritis, the development of which in a woman with cervicitis is indicated by deterioration of general health, undue fatigue, exertion, occurrence of bruises on the body, loss of healthy colour, and muddy complexion. Chronic low back ache is commonly due to cervicitis, and is commonly the prelude to infective arthritis, disappearing after removal of the cervicitis by diathermy. The results with diathermy in cervicitis are among the most satisfactory in the whole realm of therapeutics.—E. P. Cumberbatch, *Practitioner*, ii/1933, 517.

EXPERIMENTAL SYPHILIS in rabbits cured by the induction of artificial pyrexia by exposing them in the electrostatic field of a high-frequency oscillator, operating at a frequency of 10,000 kilocycles. No injurious effect on growth, mating or fertilisation, with temperatures not greater than those within physiological limits.—Carpenter, Boak and Warren, *Brit. med. J.*, i/1933, 706.

Short-wave therapy. Discussion by the Section of Physical Medicine of the R.S.M.—*Brit. med. J.*, ii/1934, 956.

Electric Shock. There is not the smallest danger of sudden death if the current enters one foot or leg and leaves by the other, but there is danger if a current at only 65 volts travels *through the thorax and so has a chance to pass through the substance of the heart*. A dry skin offers greater resistance to the entrance of electrical current than a moist one.

100 volts is thought to be dangerous—50 may be considered unsafe. The danger depends also on amperage—1/10 ampere would produce death, but, medically, persons have “endured” 1 ampere without fatal results.

The question of danger to man of electric currents may be discussed under six headings: (a) *Voltage*.—Death has occurred from shock at voltages as low as 65 with *alternating* currents. A *direct* current at 95 volts has caused death. (b) *Amperage*.—70 to 90 *m.a.* of an ordinary alternating current would be enough if the current went through the chest and heart. (c).—*Duration of the contact*. (d).—*Industrial alternating currents* are, other things being equal, more dangerous than continuous currents 2 or 3 times as powerful.—Board of Trade agrees as to this). Alternating current that reverses the direction of its flow 100 times a second is described as an alternating current of 50 *periods* or cycles a second, or as having a frequency or periodicity of 50 (cycles). The frequency is of great importance in considering its danger to life. (e).—*Position of electrodes*. The heart is the danger point. (f).—*Resistance* at the electrodes.

Treatment of Injuries Caused by Electric Currents

In case of shock, only apparent death is produced at first, and it may be possible to resuscitate by artificial respiration if used *at once*. If patient is in contact with the wire pull him away by catching hold of his *clothing* or by using a good thick layer of cloth, e.g., one's coat (*dry*), or by using a newspaper. Do not touch him unprotected—use rubber gloves if available. In any circumstances the breaking of the current means a fresh shock to the individual concerned. If in contact with a live wire this is to be cut, if possible, with long iron scissors in wooden handles.

For treatment of burns, apply boric acid compresses or charcoal poultices if there is much destruction of tissues. A common result of a severe electric shock is rupture of fine vessels in the brain. Hence, in *first aid*, *the head should be raised, not lowered*.

If a doctor on his arrival finds artificial respiration being practised he should not, because the heart-beat cannot be detected, presume life to be extinct, but should advocate perseverance in artificial respiration. It is clear that the importance of immediate application of artificial respiration in cases of apparent death from electric shock and of persistence in applying it, though generally

appreciated by electrical engineers, is not adequately realised by factory occupiers or by members of the medical profession. Both the Silvester and Schaeffer methods are applicable, the important thing being immediate application combined with inhalation of oxygen-carbon-dioxide mixture.—Form 17 Nov. 1933, Factory Dept., Home Office, per *Lancet*, ii/1934, 206.

All cases of electric shock should be treated by artificial respiration immediately after the accident.—S. Jellinck, *Arch. Radiol.*, 1927, 317.

The best explanation of deaths from electric shock is that they are due to a sensory stimulation causing paralysis of the respiratory centre, justifying artificial respiration. Many cases may be only apparent death, real death supervening from lack of means of carrying on the essential functions of the body.—Bernard Spilsbury, *Arch. Radiol.*, 1927, 316.

ACTINOTHERAPY

ULTRA-VIOLET RAYS

Finsen Lamp. This was the first source of ultra-violet light, the concentrated light being violet and ultra-violet. It is produced by an arc lamp in which the heat rays are cut off. Finsen's original lamp was superseded by the "Finsen-Reyn" lamp, and this again has given place to the:

Finsen-Lomholt Lamp, designed for the local treatment of skin lesions, especially skin tuberculosis, with concentrated carbon arc light. Its use is based on the observation that the therapeutic effect of light treatment depends almost entirely on the ultra-violet rays. By using a double colour filter it is possible to absorb not only the dark heat rays but also the luminous rays without reducing the effective ultra-violet rays by more than about 20%. By passing the carbon arc light through the filter a mixture of rays is obtained very rich in ultra-violet energy (about 75%), which, with the old apparatus did not amount to more than about 15% of total radiation energy. It is thus possible to carry out a much more intensive radiation without risk of burns, while cutting the radiation time down to about half.—Svend Lomholt, *Lancet*, ii/1933, 1034.

Tungsten Arc Lamp. The amount of ultra-violet radiation obtained from any metallic electrode appears to be directly proportional to the melting-point of the metal. Tungsten has the highest melting-point of any metal obtainable. Tungsten arc electrodes appear therefore to be the most efficient source. Radiations have destructive action on micro-organisms and cause active hyperæmia in superficial tissues. Protection of the eyes is essential.

Failure frequently due to unsuitable or inefficient apparatus. A tungsten lamp, capable of carrying 20 amperes, is the most efficient for local or general treatment. The intensity of the electrical energy is important—a 5-ampere tungsten lamp is relatively ineffective compared with a 15-ampere lamp used at a distance of from 12 to 6 inches for local treatment.—W. J. Turrell, *Br. med. J.*, ii/1932, 174.

The **carbon disulphide lamp** and the **mercury vapour lamp** also produce ultra-violet light; the latter has been developed by P. Cooper Hewitt. Schattner and Kusch enclosed the mercury

n tubes of fused rock crystal—thereby obtaining a very strong source of the light.

A resistance coil enables voltage to be adapted to the requirements of the lamp. The eyes and skin must be protected in using by an ordinary sheet of glass.

A water-cooled quartz mercury vapour lamp for the treatment of chronic inflammatory diseases of the mouth, pharynx, and larynx, by local application. The lamp emits luminous and ultra-violet rays of wave-length from about 8,000 to 2,300 A.U., the infra-red and heat rays being absorbed by the water circulation. It operates on an electric current of 1 to 1.5 amps. and 80 to 120 volts between the electrodes (direct current).—A. Eidenow, *Brit. med. J.*, ii/1933, 94.

The proportion of ultra-violet rays emitted by a lamp depends on whether it is water-cooled or not, and also upon the age of the lamp. Ultra-violet radiation is more intense as the temperature of the tube rises.

Penetrating Power of Different Rays. Those with wave-length from 2,000 to 2,400 A.U. are stopped in the stratum corneum of the epidermis: from 2,500 to 3,300 are stopped in the stratum mucosum of the epidermis: from 3,400 to 3,900 pass through the epidermis and are stopped by the blood in the subepidermal capillaries. Visible violet light rays (4,000 A.U.) probably penetrate no further than longest ultra-violet light rays, but visible red rays (7,900 A.U.) may reach the superficial strata of the muscles under the deep fascia. Visible green and yellow rays have an intermediate, and invisible heat rays a feeble penetrating power.

The human epidermis is permeable to ultra-violet radiation, from 96% to 26% transmission being found for wave-lengths from 437 m μ to 294 m μ respectively.—N. S. Lucas, *Biochem. J.*, 1931, 57.

Effect on Metabolism. Exposure of the skin of animals to ultra-violet radiation gives increased bactericidal power to the blood and serum.

Ultra-violet light has a distinct effect on cell metabolism, this effect being exerted not only locally on the skin but on deeper organs and on the general body metabolism as well.—*J. trop. Med. (Hyg.)*, 1924, 78.

Growth is promoted, it has been said, by breathing air which has been irradiated with ultra-violet light, but Webster and Hill definitely conclude that it has no effect on growth.—*Nature, Lond.*, i/1924, 761.

Ultra-violet light depresses the lipase and stimulates the protease in the blood.—per *J. Amer. med. Ass.*, ii/1925, 66.

Effect on the Skin and Body. The most potent erythema-producing rays are those from 2,900 to 3,000 A.U.: the pigment-producing rays are those from 2,900 to 3,300 A.U. Rays below 2,900 produce marked erythema without pigmentation. Amongst other important effects are the activation of cholesterol, increase of calcium and phosphorus content of blood, and of red blood corpuscles and hæmoglobin, and increased power of the irradiated body to combat infection. It is mainly by indirect action that the rays have therapeutic effect. Only in a very few diseases is local treatment of value and even in these, general treatment is of more value.

The "short" rays (2,000 to 2,400 A.U.) do not produce any biological effect, as they do not penetrate beyond the dead tissue of the epidermis—if they fell on living tissue they would destroy it to a slight depth. Although the rays 2,300 to 2,400 A.U. are the most powerfully bactericidal, they have only very feeble penetrating power. The longer the wave-length the lower the germ-destroying power, and therefore ultra-violet rays cannot destroy bacteria by direct action if they be more than the very slightest depth below the surface.

Dosage in Ultra-violet Treatment. Methods of dosage consist of (1) biological standardisation, using *infusoria*; (2) test of sensitiveness of the skin to light; and (3) effect of a test dose on the bactericidal powers of the blood. The bleaching of an acetone solution of methylene blue may be used in place of the *infusoria*.—A. Eidenow, *Lancet*, ii/1925, 317. See also A. Webster and co-workers, *Lancet*, i/1924, 745.

Pastilles of chloralformamide and diphenylamine, though originally white in colour, change to a progressively deepening yellow on exposure to ultra-violet light. The pastilles are sensitive to all radiations extending between 2,800 A.U. and 2,300 A.U. The measurement of the tint is carried out with a

tintometer. The pastilles are unaffected by diffused light and do not alter colour for some hours after exposure.—L. A. Levy and D. W. West, *Brit. Radiol. (B.A.R.P. Sect.)*, Oct. 1926, 140.

Chemical method for standardisation—the **Uroxameter**, by action of rayson a solution of oxalic acid and uranium acetate.—*Lancet*, i/1927, 353; see J. E. Moss and A. W. Knapp, *Brit. J. Actino-Therap.*, 1927; *Brit. chem. A. (A)*, 1927, 322.

Method of Exposure. The patient is divested of clothing (except genitalia) and lies on his back, with eyes protected by goggles, the lamp hanging 3 feet above middle of body, but a little to one side. First exposure 2 minutes front and back, repeated every other day, increasing exposure each time $\frac{1}{2}$ minute up to 10 minutes each front and back. This completes course. If longer course necessary, save time by bringing lamp to 2 feet and reduce exposure from 10 to 5 minutes. If erythema occurs stop treatment till it disappeared. In children start with 1 minute exposure increased by $\frac{1}{2}$ minute and in infants $\frac{1}{2}$ minute, increased by $\frac{1}{4}$ minute.

Diseases and patients in which treatment is likely to produce harmful effects. Patients with general pyrexia should not receive it. In acute local infection local rays should not be used, nor generally if body temperature raised. Omit treatment if pus present or suspected. Should not be given in pulmonary tuberculosis except by an expert. Inadvisable in case of failing heart, Bright's disease, and in very old people. Omit during menstruation.—E. Cumberbatch, *Brit. med. J.*, ii/1928, 43.

Deleterious Effects. Severe dermatitis following an artificial sun bath. H. MacCormac and H. M. McCrea, *Brit. med. J.*, i/1925, 693.

Patients with unduly low blood pressure may be intolerant to ordinary doses and develop lassitude, depression, headache, etc., but will often receive benefit from subminimal doses.—J. B. Ferguson, *Brit. med. J.*, i/1926, 403.

Skin irritation following. In the milder cases bathing the skin with alkaline lotions is effective. A routine examination of the urine is undertaken in cases showing marked acidity an alkaline mixture is given, and increased exercise in the open air, to prevent irritation which may arise from deficient alkali reserve.—S. van S. Boyd, *Lancet*, ii/1928, 1076.

GENERAL VIEWS ON ACTINOTHERAPY

Although actinotherapy cannot fulfil all the claims made for it by its sanguine exponents, there is a definite set of conditions in which its employment is indicated, and though in skilled hands it may prove valuable, improperly used it may do the gravest mischief. Properly applied, it is an important agent in the AMELIORATION OF RICKETS AND SURGICAL TUBERCULOSIS—often producing complete cure—and is of benefit in some NEUROLOGICAL CONDITIONS (e.g., anterior poliomyelitis, Bell's palsy, the root pain of tabes dorsalis, and herpes zoster), ANÆMIAS and SKIN DISEASES. But it may do definite and irretrievable harm in pulmonary tuberculosis, arteriosclerosis, chronic nephritis, quiescent appendicitis, and various forms of neurosis. Early or latent phthisis may be brought up into activity.—*Brit. med. J.*, ii/1928, 662.

Types of cases likely to benefit by light treatment in a general clinic (1) tuberculosis of bones, joints, glands of the peritoneum, lupus vulgaris of the skin and mucous membranes; (2) rickets; (3) blood disorders; (4) neurasthenia; (5) some forms of chronic arthritis; (6) *B. coli* pyelitis.—J. Sequeira and W. J. O'Donovan, *Lancet*, i/1925, 909.

Gratifying results in furunculosis, eczema, alopecia (especially alopecia areata), onychia, chilblains, Raynaud's disease, psoriasis and pruritus, also in disorders of menstruation. Relieves pain in sciatica and lumbago and other forms of fibrositis and neuritis. Its immediate analgesic effect little short of miraculous.—F. Humphris, *Practitioner*, i/1926, 380.

A valuable remedy for erysipelas and certain types of cutaneous and subcutaneous tuberculosis, also in acne vulgaris, adenoma sebaceum, pityriasis rosea, parapsoriasis, psoriasis, telangiectasis, indolent ulcers and wounds, port-wine stains; in eczema it is likely to do more harm than good, in pruritus it may actually increase the discomfort, and in the disseminate type of neurodermatitis it is extremely dangerous. Its real field is in the treatment and prevention of "surgical" tuberculosis.—G. M. Mackee, Council on Physical Therapy of the A.M.A., per *Brit. med. J.*, ii/1932, 67.

There is *no scientific reason to suppose that the supply of vitamin D to the body is better effected by ultra-violet rays than by the direct provision of the necessary food values*, and it costs three to four shillings to give by light an effective supply of vitamin D that would cost less than a penny if given as cod-liver oil. As to the power of light radiations to excite local inflammatory reactions in the skin this can be effected equally as well by a mustard plaster. It would seem to be the duty of those taking the responsibility of prescribing light treatment not only to secure that its known dangers shall be avoided, but to find and announce evidence of its benefits other than those due to commercial advocacy and popular credulity.—*Rep. med. Res. Coun., Lond., 1927-28, Lancet, i/1929, 628.* Criticisms of the Report: H. S. Banks, *Lancet, i/1929, 684*; M. Weinbren, *ibid., 685*; G. M. Levick, *Brit. med. J., i/1929, 620.*

AFFECTIONS TREATED WITH ULTRA-VIOLET LIGHT

ALOPECIA TOTALIS treated with ultra-violet rays. Cases responded well, and recovered growth of hair.—A. Eidenow, *Brit. med. J., ii/1930, 940.*

ANALGESIC EFFECT. Radiant heat and ultra-violet light are both powerful.—F. Hernaman-Johnson, *Practitioner, i/1926, 319.*

ASTHMA resistant to all other treatment cured by ultra-violet light: three cases quoted. Results probably due to leucocytosis, germicidal action, increased absorption of calcium and phosphorus and formation of vitamin D, increase of iron in the blood, rise of hæmoglobin in the erythrocytes, and increased secretions of thyroid and adrenal glands.—A. Bryce, *Brit. med. J., i/1927, 510.* The number of attacks is considerably reduced, but relapses occur in two-thirds of the cases.—*Brit. med. J. Epit., i/1927, 54.*

Infantile asthma well treated. Caution needed owing to production of ozone by quartz lamp with irritant effect on bronchi and lungs.—*Brit. med. J. Epit., i/1926, 52.*

ECZEMA.—100 cases in the Finsen Institute at Copenhagen well treated by the application of concentrated light from a carbon arc lamp. Single exposure for each spot 70 to 140 minutes of a carbon arc light of 50 amperes and 55 volts. As it is laborious and expensive, its use should be limited to resistant cases.—Svend Lomholt, per *J. trop. Med. (Hyg.), 1923, 202.*

EYE AFFECTIONS. Ocular tuberculosis in any form gives ready response. Phlyctenular ophthalmia also well treated. Infective irido-cyclitis cases show less dramatic response.—W. Stewart Duke-Elder, *Brit. med. J., i/1926, 891.*

FRACTURES. Especially where there is delay in union, a combination of ultra-violet light with direct current proved effective.—C. B. Heald, *Lancet, i/1925, 1162.*

HERPES, occurring 5 weeks after a course of Auremetine and Stovarsol, cleared up with no scarring after treatment with ultra-violet light—5 minutes at 2 ft. with the air-cooled Hanovia lamp on four successive days. In a control case not so treated the vesicles and itching persisted for 3 weeks.—M. Weinbren, *Lancet, ii/1927, 865.*

IMPETIGO CONTAGIOSA.—Slight but definite curative effect. General exposure in this complaint safer and more efficient than local exposure at short range.—J. B. Ellison, *Lancet, i/1927, 1345.*

LUPUS and other forms of tuberculosis.—A. Reyn, *Brit. med. J., ii/1923, 499.* 90% of cures obtained in lupus vulgaris and other forms of skin tuberculosis with combined treatment locally and the light bath.—*Lancet, ii/1923, 511.*

Carbon arc light in lupus. 70% of cures in the dry type at London Hospital by Finsen's method.—J. H. Sequeira, per *J. trop. Med. (Hyg.), 1923, 292.*

Of little use in lupus erythematosus.—*Brit. med. J., ii/1924, 514.* Extensive lupus cleared out completely in less than 3 months, using the Finsen-Lomholt lamp.—E. M. Holmes, *Lancet, ii/1933, 1033.*

NEURALGIA following herpes zoster well treated with ultra-violet rays.—*Prescriber, 1926, 138.*

NOSE AND THROAT diseases treated.—A. Eidenow, *Brit. med. J., i/1929, 289.* Tuberculous and other buccal pyogenic chronic ulceration, rapid healing.—A. Eidenow, *Lancet, ii/1929, 651.*

PARALYSIS, INFANTILE.—Good results with light treatment in conjunction with local treatment of the affected muscles by red rays.—G. Murray Levick, *Lancet*, i/1925, 686.

PSORIASIS. The combined treatment of psoriasis with crude coal tar ointment and exposure to ultra-violet quartz lamp better than either treatment alone. The ointment is applied to patches for 24 hours and removed with olive oil. The light is applied for one minute at a distance of 30 inches, and the time increased one minute daily for 3 or 4 days.—per *J. Amer. med. Ass.*, ii/1925, 21.

PYORRHŒA with systemic infection. Erythema dose of ultra-violet rays administered to trunk, a specific cure.—*Brit. med. J. Epit.*, ii/1926, 101.

Beneficial results by use, in conjunction with ultra-violet rays, of 1% eosin in pyorrhœa alveolaris, of 5% protargol in skin diseases, and of saline in tuberculous and rickets.—G. Matteucci, *The Limitations and Defects of Actinotherapy*.

RHEUMATIC DISEASE (chronic). Beneficial. Local analgesic powers considerable in neuritis, fibrositis, and arthritis.—A. G. Watson, *Prescriber*, 1926, 412.

RICKETS. The rays the most active and most powerful treatment in early childhood.—*Brit. med. J. Epit.*, i/1925, 8. See also F. H. Humphris, *Lancet*, i/1925, 912.

Rickets treated with artificial sunlight reinforced by administration of eosin.—*J. Amer. med. Ass.*, i/1926, 1407. (1 grain doses have been used.)

TUBERCULOSIS. A valuable adjunct to other treatment.—H. Godde, *Lancet*, ii/1923, 238. Whole body exposed gradually to the light from short flame carbon arc lamps consuming 75 amps. For patients who are receiving maximum dosage of 2 or 2½ hours it is not economical.—G. B. Dixon, *Brit. med. J.*, ii/1925, 473.

Review of treatment of peritoneal and glandular tuberculosis in children by ultra-violet rays during last few years. The authors conclude that (1) the successful use of ultra-violet rays has been of decided value in peritoneal, glandular and osseous tuberculosis, (2) mesenteric glandular tuberculosis is the most rapidly improved, then mediastinal and lastly peripheral glandular tuberculosis, (3) pulmonary miliary tuberculosis, even in early stage, is unaffected.—*Brit. med. J. Epit.*, i/1925, 3.

All forms of tuberculosis, except pulmonary and meningococcal, in which it is contraindicated, are benefited—fresh air an important adjunct.—per *J. Amer. med. Ass.*, ii/1925, 1091.

The original idea that artificial heliotherapy would prove an almost specific treatment for surgical tuberculosis has not been justified. A series of cases thus treated showed no marked improvement over those not so treated. Artificial heliotherapy does not change the fundamental principles of treatment of surgical tuberculosis.—E. C. Mekie, *Brit. med. J.*, ii/1928, 243.

Genito-urinary tuberculosis: of value. Treatment lasts for 2 years.—*Brit. med. J. Epit.*, i/1925, 12.

TUBERCULOUS LARYNGITIS at Copenhagen; disease arrested in 50% of cases.—*Lancet*, ii/1923, 512; O. Strandberg, *Lancet*, ii/1923, 1237.

Treatment by the Kromayer model No. 2 water-cooled mercury arc vapor lamp, with a quartz laryngeal applicator designed by Dr. William Beaumont shows promising results, but is probably best employed as an adjuvant to other methods of treatment.—R. Scott Stevenson, *Brit. med. J.*, ii/1933, 964.

Results of light treatment, using the carbon arc lamp, on laryngeal tuberculosis at the Vejlefjord Sanatorium (Denmark). Percentage of healing in 257 patients 59.4%. The prognosis of a laryngeal lesion as a complication of phthisis is no longer to be considered so gloomy as hitherto supposed. A great majority can be helped by a combination of light treatment, endolaryngeal intervention, and sanatorium régime, including all the available methods of active lung treatment.—O. Strandberg and J. Gravesen, *Lancet*, i/1934, 128.

Sunlight. No artificial source of radiation yet found which has a spectral energy distribution exactly like that of sunlight; that of the carbon arc is the closest approach, but even that contains ultra-violet light of very short wave-lengths and infra-red radiation of long wave-lengths not found in sunlight; it also

mits an intense violet radiation in excess of that in sunlight.—*J. Amer. med. Ass.*, i/1929, 836.

The importance of skyshine: the sky is the most valuable source of ultra-violet rays. Bright clouds and blue sky give more ultra-violet radiation than the high sun and far more than the low sun.—Leonard Hill, *Brit. med. J.*, i/1926, 618.

Sunlight and artificial sunlight. Influence on health. Owing to smoke pollution in cities, the ultra-violet rays are cut down by half, and even two-thirds, in comparison with country and seaside places.—L. Hill, *Brit. med. J.*, ii/1925, 71.

The Acetone-Blue Gauge shows that on the average two-thirds of the ultra-violet rays are cut off by smoke and dust pollution of the atmosphere in the City of London.—*Rep. med. Res. Coun., Lond.*, 1925-6, *Lancet*, i/1927, 508.

Sun Cure of Tuberculosis. Good effects from the sun cure of tuberculosis can only be obtained by means of exact medical observation and supervision. The patient should be slowly acclimatised to the sunshine, starting with 5 minutes exposure of the legs only, and slowly increasing daily until in 12 days a complete sun-bath of an hour's duration is allowed. Results of treatment remarkably good. In unfavourable weather artificial sunlight is given.—*Lancet*, i/1923, 237.

The only untoward result seen in light-bath treatment is the occasional "flare up" of a tubercular process, especially where there is pyrexia. Wise to begin treatment of visceral tuberculosis with very short exposures limited to small areas. It is generally accepted that patients whose skin pigments best make the most rapid and complete recoveries, though the pigmentation is probably only an index of some chemical change in the blood.—J. H. Sequeira, *Brit. med. J.*, ii/1924, 515.

When undertaken not under medical advice, insolation is suitable only for the well man who feels the better for it. For the sick and infirm it should never, under any circumstances, be undertaken except under medical supervision. The sun cure should be regarded merely as an adjuvant treatment in non-pulmonary tuberculosis. While advocating the treatment, the author utters a warning that it must be wisely and carefully employed—gradual exposures are essential.—Sir H. J. Gauvain, *Brit. med. J.*, ii/1924, 234.

The dangers of misapplied sun-cures.—Lennox Wainwright, *Practitioner*, i/1924, 197.

Sunbathing. Details of 11 cases, with the onset or exacerbation of symptoms of pulmonary tuberculosis following sunbathing. It is dangerous for anyone who has had hæmoptysis to sunbathe until tuberculosis of the lungs has been excluded, or for people who have recently lost weight, feel abnormally tired, or have other suspicious symptoms. Sunbathers who feel tired or feverish, or perspire at night after a sunbath should take no more sunbaths if their evening temperature is above 99°F.—A. H. Gosse and G. S. Erwin, *Brit. med. J.*, i/1934, 15.

★ **Vitaglass** (T.M. 457402 Class 15) and "**Rest Light**" are types of glass which permit the passage of ultra-violet light.

The transparency of glasses to ultra-violet light. The following percentage transmission was obtained. With no cover, 100; with silica 0.11 inch thick, 85.7; with "Vitaglass" 0.065 inch thick, 20.8 to 24.4; with window glass 0.082 inch thick, 3.1; with "Calorex" glass 0.2 inch thick, none; and with non-actinic glass 0.2 inch thick, 0.4. Results bear out the claims made for the materials.—*Brit. chem. Abstr.*, 1927, 323.

By measuring the ultra-violet intensity from the sky-line at the window-sill and comparing the intensity of illumination at the window-sill with that in the centre of the room, it has been found that only 1/120 of the north sky ultra-violet light reaches the middle of the room, i.e., a child would have to sit in this position for 20 hours to receive as much ultra-violet light as he would receive from 2 minutes out of doors in the noon sunlight. Cheaper and more efficient to give children a short noon-day recess than to invest in special window-glass.—*Lancet*, ii/1928, 890.

Experiments at Smethwick for a year on 240 schoolchildren, proved that apart from slight increase in hæmoglobin in children of "Vitaglass" window glasses, the benefit was small, the probable reason being that the children had little of their skin exposed. Open-air schools preferable.—per *Lancet*, ii/1929, 98.

"Vitaglass" exposed to sunlight undergoes slight diminution of transparency to shortest wave-lengths for 9 months or less period.—"Vitaglass" Marketing Board, *Lancet*, ii/1929, 690.

In buildings other than those designed specifically for sun treatment, although ultra-violet glass in large, unobstructed windows can admit therapeutic radiation in appreciable quantity, to receive this radiation it is necessary to sit near a window or in the direct rays of the sun.—"Ultra-violet Window Glazing" H. E. Beckett, *Building Research Bulletin*, No. 8.

A Practical Window for Transmitting Ultra-violet Rays from Sunlight. A cheap, practical, and effective window for the purpose may be made from cellophane. The cellophane is reinforced by being sandwiched between two layers of coarse chicken wire affixed to a wooden frame (1 to 2 inch mesh wire being used), and will last for a year. The material allows the short (curative) light-waves to pass. Glass used for the purpose loses a lot of transparency by exposure.—A. H. Pfund, *J. Amer. med. Ass.*, ii/1928, 19.

Windolite. A cellulose and wire netting product allowing ultra-violet rays to pass through freely.

Infra-Red Rays have much greater power to penetrate tissues than ultra-violet rays. They cause marked vasodilation, a progressive increase in temperature of plasma, and in addition exercise a remarkable analgesic effect. They give rise to intense hyperæmia with redness of skin in zone irradiated, usually persisting for 2 to 3 hours.—*Brit. med. J. Epit.*, i/1926, 26.

Therapeutic Uses of Infra-Red Rays by W. Annandale Troup (The Actin Press, Ltd.).

"Grenz" or "Infra-Röntgen" rays, a new form of actinotherapy. These rays are situated between the ultra-violet and Röntgen rays and have a wave-length of 1.2 to 2 Angstrom Units. One unit of "Grenz" rays produces a mild erythema from 12 to 24 hours after exposure: redness disappears in 10 days and dose can be repeated every 2 weeks for several doses. Most diseases require doses of 2 units. Special low-tension apparatus ranging between 5,000 and 9,000 volts necessary. Of value in skin diseases.—per *Prescriber*, 1928, 321.

PROPRIETARY MEDICINES

The first important move in the effort to control the advertisement and sale of proprietary medicines for which extravagant therapeutic claims are made, was the publication by the British Medical Association of *Secret Remedies: What they cost and what they contain* (1909), followed by *More Secret Remedies* (1912). (Both these works are now out of print). In 1912 the House of Commons appointed a Select Committee to enquire into the conditions prevailing in the United Kingdom regarding the sale of Proprietary Medicines.

The report of the Committee was issued in 1914 and was reprinted as a supplement to the *Lancet*, Jan. 10, 1925 ("Sale of Patent Medicines"). It was found that the existing law offered no check to gross abuse of the public and recommended that the administration of the law governing the advertisement and sale of patent, secret and proprietary medicines be part of the functions of the Ministry of Health.

The Committee considered that the exhibition of formula—a much discussed proposition—"does not appear to us to be a proper practical or effective measure" (except in the case of alcohol, poisons and certain dangerous drugs). Further, that pure drugs, vendued entire under fancy names, should no longer be exempt from duty, that the distinction between the name of an ailment and the name of an organ, the seat of that ailment, should be abandoned, and that the exemption should not apply to medicines generating carbonic acid gas. It was also recommended that reference to the patent medicine stamp in advertising matter should be prohibited and that no name of a proprietor or firm should be printed on the stamp. The report also dealt with the law relating to proprietary medicines in the British Dominions, Germany, Austria, Hungary, France and Italy.

U.S.A. Proprietary Medicines. The Department of Agriculture, through the Bureau of Chemistry, has issued details as to claims of therapeutic effects, indefinite and sweeping terms, testimonials, etc., for guidance as to wording of labels permissible under an Amended Food and Drugs Act. Such names as "Nerve Tonic," "Lung Balm," "Kidney Pills" are objected to. Guarantees as to refund of money also are not permissible.—*Brit. med. J.*, i/1915, 24.

The Food and Drug Administration of the Department publishes in bulletins issued at frequent intervals reports on "patent medicines" whose sale has been found to violate the Food and Drugs Act. These reports are summarised in the *J. Amer. med. Ass.*

Proprietary Medicine Bills.

In July 1920 a Bill, based on the recommendations of the Select Committee, was introduced into the House of Lords. Among the proposals were the prohibition of the sale or advertisement of remedies purporting to treat or cure certain diseases, the registration of proprietary medicines and their owners, and the disclosure of the formulæ of all such preparations.

A Proprietary Medicine was defined as any medicine held out advertisement, label or otherwise in writing as efficacious for the prevention, cure or relief of any malady, ailment, infirmity or disorder affecting human beings and

(a) which is sold under a trade name or trade mark to the use of which any person has or claims or purports to have an exclusive right; or

(b) of which any person has or claims or purports to have an exclusive right of manufacture or for the making of which any person has or claims or purports to have any secret.

For an analysis of the provisions of the Bill as amended in the Committee of the House of Lords, see *Chem. & Drugg.*, ii/1920, 1472; see also *ibid.*, ii/1920, 1503, and i/1921, 49.

Throughout the discussions on the Bill exception was taken to the disclosure of formulæ of proprietary medicines, but the position in this respect has now been altered completely "De-stamping" (see below).

After reaching the Report stage in the House of Lords the Bill was not proceeded with on account of the dissolution of Parliament. A further Bill, with essentially the same provisions, was drawn up by the Health Advisory Committee of the Labour Party and introduced in the House of Commons in May 1931, but afterwards withdrawn.

Since 1920 many things have happened—the D.D.A. control of narcotics, the Labelling of Poisons Order, requiring the proportion of poisons to be stated on the label; the formation by the newspapers of a Committee which watches over all patent medicine advertisements; but the position of the patent medicine trade is not creditable to either doctors or pharmacists. The Parliamentary Committee on Food and Health are endeavouring to frame a non-controversial Bill which would deal with the serious side of the patent medicine trade. H. N. Linstead, *Pharm. J.*, i/1933, 411.

At the request of the Standing Committee on Scientific Research of the Economic Advisory Council, the Council of the Royal College of Surgeons has given their views on patent medicine legislation, the following being abstracted from a statement appearing in the 1934 Annual Report of the College.

A Bill is at present being considered by the Parliamentary Committee on Food and Health, the object of which is to prohibit the advertisement and sale of medicines or appliances for the prevention, cure or relief of certain diseases and conditions, the use of fictitious testimonials and the offer of diagnosis and treatment by correspondence. The representatives of the patent medicine trade declined to support any Bill on the lines of the Select Committee but agreed not to oppose a measure such as has now been drafted.

In the opinion of the Council the problem can only be adequately dealt with on the lines of the Select Committee of 1914 by bringing the sale of proprietary medicines and appliances under the control of the Ministry of Health. Such control should ensure: (1) That the article is not injurious. (2) That the description of its therapeutic action is not fraudulent. (3) That the sale of the article and the method of its advertisement are not against the public interest. (4) That no medicine or appliance is advertised as a cure for any of the following diseases and conditions:—Blindness, Bright's disease, cancer, consumption, diabetes, epilepsy, fits, locomotor ataxy, lupus, paralysis.—Per *Brit. med. J.*, ii/1934, 8.

In Canada a proprietary or patent medicine is defined by the Proprietary or Patent Medicines Act as "any artificial remedy or prescription manufactured for the internal or external use of man, the main composition or definition of which is not to be found in the *British Pharmacopœia* . . . or other recognized and approved pharmacopœias or formularies . . . or upon which is not printed in a conspicuous manner the true formula or list of medicinal ingredients contained in it."—*Pharm. J.*, ii/1934, 590.

Proprietary Medicines and Revenue

The immense increase in the sale of patent medicines since the Select Committee was appointed is indicated by the fact that in 1929 the *revenue alone* from Patent Medicine Stamps reached a maximum of £1,333,512, whereas Dr. Cox, before the Select Committee (1912), made the statement (*Chem. & Drugg.*, i/1912, 923) that £2,500,000 had been *spent by the public* on patent medicines since 1908. The number of patent medicine licence holders has increased from 29,000 in 1903 to 190,000 in 1934. Since 1929 the yield from the duty has rapidly decreased owing to the practice of *De-stamping*, and amounted only to £882,006 in 1933.

In order to secure the benefit of the exemption from duty of known, admitted and approved remedies when sold by chemists or those having served a regular apprenticeship, the Commissioners of Customs and Excise now require on labels, cartons, etc., a "definite and complete statement of ingredients (i.e., the full formula with proportions) and a statement that no proprietary rights are claimed in the preparation of the medicine."—*Pharm. J.*, i/1930, 238.

Numerous manufacturers of patent medicines now supply, for sale by chemists, unstamped articles the formula of which is printed on the label; such preparations are vended as, say, "—— Brand of Cough Mixture." The brand name is registered as a trade-mark, which confers proprietary rights on the *name*, although the label bears some statement in accordance with the above requirements of the Commissioners such as "Proprietary rights are not claimed in the formula or method of preparation of this article except in the registered trade mark." The majority of extensively advertised proprietary medicines are now sold unstamped under brand names, the formulæ being disclosed.

Once a preparation is liable to stamp duty it is always liable, but formulæ are altered in order to evade this rule.—J. Humphrey, *Pharm. J.*, i/1930, 165.

One important effect of the above ruling of the Commissioners of Customs and Excise is to make dutiable preparations recommended for the treatment of a disease even if made according to formulæ published in well-known books of reference (such as the *B.P.*, *B.P.C.* and the *Extra Pharmacopœia*) and labelled as such without further disclosure of formula. This is contrary to the decision in the *Farmer v. Glyn-Jones* test case (1903) in which it was held that Ammoniated Tincture of Quinine B.P. could be sold unstamped although recommended for the treatment of influenza and colds.—*Chem. & Drugg.*, i/1930, 300.

FORMULÆ OF PROPRIETARY MEDICINES

In the following list we provide information on the composition of a large number of proprietary medicines as sold in this country. When the preparation has a brand name the formula given below is that disclosed on the label or carton without any translation or interpretation of the names of the ingredients. The identity of a common substance is often more or less disguised by the use of a complex chemical name and the exact identification of a particular ingredient is sometimes made more difficult by the omission of any indication of the structural position occupied by the substituent groups. The formulæ of many branded medicines such as pills, tablets and powders are expressed as percentages and in order to give some indication of the doses of the constituents

contained in each unit, the average weights of the units are included. These have been determined from an examination of packages obtained through the usual trade channels. In other cases where the composition has not been disclosed by the makers the information has been taken from the *British Medical Journal* and the *Lancet*; reference to the pages of these journals is made in each instance and the reader is referred to the original sources for further details. The majority of those to which *Brit. med. J.* references are given were described in *Secret Remedies* and *More Secret Remedies*, and in a few instances these books are given as the only references. The formulæ of a number of proprietaries as offered for sale in Italy are taken from *Lancet*, i/1924, 256.

The composition of a proprietary article in one country does not necessarily convey a correct impression of an article sold under the same name in other countries.—*Brit. med. J.*, i/1910, 339.

Agarol Brand Compound (*William R. Warner & Co., London*).—Described as a perfectly homogenized emulsion, each fluid ounce containing Mineral Oil, Heavy, 152 m.; Phenolphthalein, 6 gr.; Glycerin, 52 m.; Glycerite of Boric acid, 14 m.; Agar Jelly, 92 m.; Acacia, Purified No. 1, 4·6 gr.; Tragacanth, Purified No. 1, 1·7 gr.; Sodium Benzoate, 2·2 gr.; Distilled Water, sufficient to make 1 fluid ounce.

Alepsal (*Genevrier, Neuilly; Wilcox, Jozeau & Co., London*).—Each tablet contains Phenylethylmalonylurea, 0·1 g.; Powdered Belladonna, 0·02 g.; Trimethylxanthine, 0·025 g.

Allcock Brand Porous Plaster (made in U.S.A., European agency:—*The Allcock Manufacturing Company, Birkenhead*).—(For rheumatism, neuritis, etc.)—Rubber, 43·39%; Burgundy Pitch, 27·14%; Frankincense, 20·25%; Orris Root, 8·70%; Capsicum, 0·27%; Beeswax, 0·18%; Camphor, 0·04%; Gum Elemi, 0·02%; Gum Myrrh, 0·01%.

Alzam Brand Ointment (*N.D.K. Laboratories Ltd., London*).—(For wounds, insect bites, eczema, impetigo, etc.)—Phenol, 9%; "Acidum Cresilicum," 1%; Meth. Sal. 5%; Ol. Cedris, 2%; Ol. Eucal., 3·5%; Lanoline, 2%; Ol. Picis, 4%; Stearine Excipients, 73·5%.

Anadin Brand Tablets (*Anadin Ltd., London*).—Each tablet contains Acetphenetidin, 3 gr.; Acetylsalicylic Acid, 3 gr.; Caffeine Alkaloid, $\frac{1}{4}$ gr.; Quinine Sulphate, $\frac{1}{4}$ gr.

Anestan Brand Tablets (*The Anestan Co., London*).—(For asthma, headache, fever, etc.)—The average weight of each tablet is about $3\frac{3}{4}$ gr. Formula in mg.: Disodiofluorescein, 0·5; Calc. Gluconate, 2·0; Amylodextrin, 2·5; Theophyllin, 4·0; Maranta, 4·0; Ephedrine Hydroch., 8·0; Dimethylaminophenyldimethylpyrazolon, 32·0; Theobromin., 12·0; Amylum, 35·0.

Angiers Brand Emulsion (*Angier Chemical Co., Ltd., London*).—Paraffinum Liquidum, 160 m.; Calcii et Sodii Hypophosphis, 9·05 gr.; Glycerinum, 52 m.; Sodium Benzoas, 1·25 gr.; Muc. Acaciæ et Aqua destillata, q.s. ad 1 oz.

Animasa (*Organotherapeutic Laboratories, Osnabrück, Germany; H. W. Braun, London*).—(For the treatment of arterio-sclerosis).—"Each tablet contains 0·05 gm. prepared extract of intima and media with decomposed products of blood corpuscles and serum."

Antexema (*The Castle Laboratory, London*).—Soft Paraffin, 35·4; Boric Acid, 1·5; Gummy matter, 12·4; Water, 50·7.—*Brit. med. J.*, i/1908, 942.

Antexema Granules (*The Castle Laboratory, London*).—Calcium Sulphide, 0·06.—*Lancet*, i/1924, 256. (As sold in Italy.)

Antikamnia Brand Analgesic Tablets (*Antikamnia Remedy Company, Distributors: Fassett & Johnson Ltd., London*).—Each tablet weighs about 10 grains and contains Phenylacetamide, 60%; Caffeine Citrate, 9·5%; Soda Bicarbonate, 30·5%. Also supplied with Codeine, each tablet containing 2·5% ($\frac{1}{8}$ gr.) of Codeine Sulphate.

Antiphlogistine Brand Dressing (*Denver Chemical Mfg. Co., London*).—Glycerinum, 45·000%; Iodum, 00·0010%; Acid Boricum, 00·100%; Acid Salicylicum, 00·020%; Menthæ Ess. 00·002%; Methylum Ess., 00·002%; Eucalypti Ess., 00·002%; Kaolin, 54·864%.

Antipon (*Antipon Company, London*).—(For obesity).—Contained: 39 gr. per ounce of Citric Acid.—*Brit. med. J.*, ii/1907, 25.

Antipon (Brand) Obesity Tablets (*The Antipon Company, London*).—Each tablet weighs about 0.25 g. ($3\frac{1}{2}$ gr.), the composition being Ext. Fuci Vesic. Sicc., 9 g.; Ext. Frangal Sicc., 5 g.; Ext. Rham. Pursh. Sicc., 5 g.; Ext. Aloes, 2 g.; Ext. Rhei, 1 g.; Pulv. Carrageen, 1 g.

Anusol Brand Hæmorrhoidal Suppositories (*William R. Warner & Co., London*).—Bism. Oxygal., 0.64 g.; "bism.-oxyiodo-resorcin. comp.," 0.55 g.; Zinc Oxid. Pur., 3.77 g.; bals. Peruv., 1.00 g.; Ol. Cacao, 17.10 g.; Ung. Cerei Borat., 7.60 g. for 10 suppositories.

Anzypan Brand Enzyme Compound (*Norgine, Prague; Napp, London*).—Stated to "contain the ferments Trypsin, Gall, Lipase, Diastase, and Pepsin."

Arcanol (*Schering Ltd., London*).—Tablets each containing $7\frac{1}{2}$ gr. of Acetylsalicylic acid and $7\frac{1}{2}$ gr. of "Atophan" Methylester.

Archanium (*The Phenolaine Company, London*).—Stated to be "an ortho-hydroxy-benzoate containing an additional carboxy methyl group, and was formerly prepared from the bark of salix repens (a form of dwarf willow which grows on heaths on mountain sides) and the dry distillate of the twigs."

Atkinson's Infants' Preservative (*Robert Barker & Son, Ltd., Manchester*).—Analysis showed in 100 by measure:—Potassium Bicarbonate, 1.75; Magnesium Carbonate, 5.45; Essential Oil, about 0.06; Alcohol, 7.0 by measure; Sugar, 9.9; colouring matter, a trace.—*Brit. med. J.*, i/1912, 683.

Bass Brand Gout and Rheumatic Pills (*Bass Brand Pill Co., Nottingham*).—The average weight of each pill (uncoated) is about 7 gr. The formula is:—Colch. Corm., 70%; Chalcantum, $3\frac{1}{3}\%$; Pulv. Ipecac. Co., $3\frac{1}{3}\%$; Ext. Colch. Acet., $13\frac{1}{3}\%$; Acacia, $6\frac{2}{3}\%$; Tragacanth, $3\frac{1}{3}\%$.

Baxen Brand Tablets (*E. Griffiths Hughes, Manchester*).—Each tablet contains Phenyl dimethylisopyrazolone, 0.0551 g.; Dimethylamidophenyl dimethylisopyrazolone, 0.0715 g.; Trimethylxanthine, 0.0227 g.; Acetparaphenolide, 0.0680 g.

Béatol Tablets (*Laboratoires Lobica, Paris; Continental Laboratories, London*).—Each tablet contains Diethylmalonylurée, 0.18 g.; Extrait de Valériane, 0.1 g.; Extrait de Jusquiame, 0.02 g.

Beecham's Brand Powders (*Beecham's Pills Ltd., St. Helens*).—The average weight of each powder is about 8 gr. The formula is Acetphenetidinum B.P., 54.240%; Quininae et Aethylis Carbonas B.P., 10.848%; Caffaina B.P., 0.848%; Magnesii Carbonas Levis B.P., 21.696%; Saccharinum Solubile B.P., 0.602%; Oleum Cinnamomi Ver., 1.766%.

Beecham's Brand Lung Syrup (*Beecham's Pills Ltd., St. Helens*).—Liq. Ext. Scillæ, 1.25%; Glycerinum, 9.8%; Tinct. Capsici, 0.052%; Olea Essentialia, 0.08%; Sodii Benzoas, 0.91%; Ammonii Carbonas, 1.140%; Ammonii Bromidum, 0.456%; Tinct. Bryoniæ, 0.416%; Tri. Chlor. Methane, 0.312%; Chloric Ether, 1.25%; "Laevulose Glucose," 44.125%; Sucrose, 33.208%; Infusion Senegæ, ad 100%.

Beecham's Brand Pills (*Beecham's Pills Ltd., St. Helens*).—Freed from coating the average weight of each pill is about 1.2 gr. The formula is:—Pulvis Zingiberis, 25.797%; Pulvis Coriandri, 5.549%; Sapo Purus, 10.235%; Aloe, 53.406%; Oleum Juniperi Bacc., 1.881%; Oleum Rosmarini, 1.951%; Oleum Anisi, 0.479%; Oleoresina Capsici, 0.117%; Oleoresina Zingiberis, 0.585%.

Beecham's Cough Pills (*Beecham's Pills Ltd., St. Helens*).—Results of analysis pointed to the formula:—Morphine, 0.0035 gr., Powdered Squill, 0.1 gr.; Powdered Aniseed, 0.3 gr.; Ammoniacum, 0.3 gr.; Extract of Liquorice, 0.4 gr.—*Brit. med. J.*, ii/1908, 1699. The composition has been altered from time to time. Originally they contained some Morphine, then to comply with the Pharmacy Act this was removed. It has been replaced in trivial amount and the pills need not be labelled "Poison."—Sir Joseph Beecham, P.M.C.E., *Pharm. J.*, i/1913, 102.

Bell-Ans (formerly **Bell's Pa-Pay-Ans**) (*Bell & Co. (Inc.), Orangeburg, New York; Christy, London*).—Papain, 0.06; Vegetable Charcoal, 0.06; Bicarbonate of Soda, 0.06; Oil of Peppermint, 0.002; Oil of Gaultheria, 0.002.—*Lancet*, i/1924, 256. (As sold in Italy.)

Beltona Brand Lotion (*Beltona Ltd., Hoddesdon, Herts.*).—Liq. Ammonia, 0.3; Oleum Citronellæ, 0.3; Oleum Verbenæ, 0.1; Methyl Salicylas, 0.3; Castor Oil, 0.9; Alcohol (Industrial), 94.8; colouring, 0.3.

Bengué's Balsam (*Bengué & Co. Ltd., London*).—Analysis showed composition to be:—Menthol, 18; Methyl Salicylate, 20; Anhydrous Lanolin, 54; and a fat, apparently Lard, 8%.—*Brit. med. J.*, ii/1910, 986.

Betul-Ol (Huxley Brand) (*Anglo-American Pharmaceutical Company Ltd., Croydon*).—Menthol, 2·2; Chloral Hydrate, 2·1; Oil of Spike Lavender, 2·0; Methyl Salicylate, 86·5; Ol. *Betula Lenta*, 7·2.

Bilax Brand Laxative Pills (*Foster-McClellan Co., London*).—Freed from coating the average weight of each pill is about 1·4 gr. The formula is Leptadrin, 8·333%; Aloin, 16·667%; Podophyll. Res., 13·333%; Jalapæ Res., 8·333%; P. Fruct. Capsic., 2·083%; Ol. *Mentha P.*, 1·333%; Oleores. Zingib., 4·445%; Excip., 45·473%.

Bile Beans (*C. E. Fulford Ltd., Leeds*).—Average weight 2·3 gr. Examination showed Aloin, Powdered Cardamoms, Oil of Peppermint, Wheat Flour, and possibly presence of Colocynth.—*Brit. med. J.*, i/1911, 1326.

Birley Brand Fortified Phosphorus (*Gordon, Murray & Co. Ltd., London*).—Each fluid ounce contains Ammonii Phosphas, 2 gr.; Ammonii Hypophosph., 2 gr.; Calcii Glycerophosph., 2 gr.; Potass. Glycerophosph. 50%; Sod. Glycerophosph. 50%, a.a. 5 m.; Free Phosphorus (Sat. Sol. in S.V.R.) ½ m.; Syrup, to 1 fluid ounce. Preparations are also supplied under the name Plain Phosphorus, Ironised Phosphorus, Bronchial Phosphorus, and Rheumatic Phosphorus.

Bisuroids Laxative Tablets (*Bismag. Ltd., London*).—Each tablet weighs about 5 gr. and contains Phenolphthalein, 40%; Sucrose, 40%; Theobromine Paste, 20%.

Blair's Gout and Rheumatic Pills (*Prout and Harsant, London*).—Makers now state that each pill contains 2 gr. of Powdered Colchicum Corm.

Blanchard's Pills (*Leslie Martyn Ltd., London*).—Freed from coating the pills had an average weight of 1·9 gr. Analysis showed presence of Sulphate of Iron, Soap, Barbadoes Aloes, Powdered Ginger, Cardamom, and Cinnamon, also a little Apiol.

Bow's Liniment. *Syn. Anodyne Liniment.* Dr. Bow's formula: Ha. Soap, 4; Opium, 8; Ammoniated Camphor Liniment, 60; macerate and filter. Dr. Bow's modified formula is Ammoniated Camphor Liniment, 6; Belladonna Liniment, 1; Soap Liniment, 6; Strong Ammonia, 1; Tincture of Opium, 1; Mix, stand 7 days, and filter. These and other formulæ are given.—*Pharm. J.*, 1907.

The preparation is stated on the label to contain 1% of Extract of Belladonna B.P. and 0·18% of Morphine.

Box's Pills (see also **Golden Fire**) (*W. H. Box, Plymouth*).—Average weight 2½ gr. The following formula gave a pill substantially agreeing in character with the pill under examination.—Powdered Capsicum, 35; Powdered Gentian, 15; Flour, 15; Aloes, 20; Soap, 5; Water to 100 parts.—*Brit. med. J.*, ii/1910, 987.

Brandreth (Dr.) Brand Pills (*Allcock Manufacturing Co., Birkenhead*). Each pill contains Aloes, 0·055 g.; Cascarin, 0·030 g.; Res. Guiac., 0·021 g.; Acacia, 0·007 g.; Ext. Sarsæ, 0·005 g.; Sapo Dur., 0·004 g.; Capsicum, 0·003 g.

Bromidia (*Battle & Co., St. Louis, Mo.; prepared in England by Roberts and Co., London*).—Each fluid oz. contains Chloral Hydrate (B.P.), 91 gr.; Bromide of Pot., 91 gr.; Cannabis Indica (Sol. Ext.) (B.P.), 1 gr.; Hyoscyamine (Sol. Ext.) (B.P.), 1 gr. It contains 10% of Alcohol.

Brown's Bronchial Troches (*John I. Brown & Son, Boston, Mass.*). Chemical analysis and microscopical examination showed the presence of Powdered Cubebs (also possibly Extract), about 6%; Extract of Liquorice in small quantity, Gum and Sugar (about 70%).—*Brit. med. J.*, ii/1911, 1543.

Burgess' Lion Ointment (*E. Burgess, London*).—The following is similar: Lead Plaster, 13; Beeswax, 20; Resin, 11; Olive Oil, 12; Water, 6; Lard, to 100. —*Brit. med. J.*, ii/1907, 393.

Burgess' Lion Pills (*E. Burgess, London*).—Average weight 4½ gr. without coating. Examination indicated Ipecacuanha, Rhubarb, a little Jalap, probably Aloes (Socotrine), Oil of Peppermint and Soap.—*Brit. med. J.*, i/1911, 1327.

Cadum Ointment (*Omega Ltd., London*).—Oxide of Zinc, 15·0%; Sulphur, 6·0%; Cade Oil, 4·0%; Salicylic Acid, 0·75%; Methyl Salicylate, 0·25%; Petrolatum, 74·0%.

Cal-Bis-Nate (*William R. Warner & Co. Ltd., London*).—Makers state that each level teaspoonful contains approximately Calcium Carbonate, 9 gr.; Bismuth

Subgallate, 1 gr.; Bismuth Subcarbonate, 2 gr.; Magnesium Carbonate, 5 gr.; Sodium Bicarbonate, 10 gr.; Colloidal Kaolin, 3 gr.

California Syrup of Figs Brand Laxative (*Proprietary Agencies Ltd., London*).—"Syrup. Ficorum California," 33·29%; Ext. Cassia Acutifolia, 27·84%; Sacchari Alb., 38·7%; Ol. Cinnam., 0·04%; Ol. Menth. Pip., 0·08%; Ol. Caryoph., 0·11%; Ext. Gingib., 0·11%; Aq. Puræ, q.s.

Capsuloids (*Capsuloids* (1909) *Ltd., London*).—Result of analysis indicated for the contents of the capsules:—Hæmoglobin, 1·97 gr.; Olive Oil and Oleic Acid, of each 0·54 gr.; Balsam of Peru and Purified Storax, 0·17 gr. in one capsule.—*Brit. med. J.*, i/1908, 833.

Carmarole Brand Compound Tablets (*International Laboratories Ltd., London*).—Extract of Barosma betulina, $\frac{1}{4}$ gr.; Potassii Nitras, 1 gr.; Extract of Bearberry Leaves, $\frac{1}{4}$ gr.; Resina Podophylli, $\frac{1}{8}$ gr.; Oleum Bacc. Juniper, $\frac{1}{8}$ m.; Hexamethylene-tetramine, $\frac{1}{2}$ gr.; Oil of Barosma betulina, 1/25 m.

Carnrick's Liquid Peptonoids (*G. W. Carnrick Co.; Brooks & Warburton Ltd., London*).—100 parts contained Alcohol, 20; Total Solids, 18·8; Nitrogen, 0·8 (equivalent to Protein, 5·0); Ash, 0·8; Reducing Sugar calculated as Glucose, 7·7; Cane Sugar, 2·4.—*Brit. med. J.*, ii/1909, 562.

Carter's Brand Little Iron Pills (*Carter Medicine Co., London*).—Freed from coating, the average weight of each pill is about $\frac{1}{2}$ gr. The formula is Ferrous Carbonate Mass, 0·875 g.; Zinc Phosphide, 0·0025 g.; Manganese Dioxide, 0·25 g.; "Cascarin Bitter," 0·125 g.; Excipients, q.s.

Carter's Brand Little Liver Pills (*Carter Medicine Co., London*).—Freed from coating, the average weight of each pill is about $\frac{1}{2}$ gr. The formula is Podophylli Resina, 0·0625; "Aloe Curaco," 0·25; Glycyrrhizae, 0·00238; Acaciae, 0·006; Amylum, 0·017; Excipients, q.s.

Carter's Brand Little Nerve Pills (*Carter Medicine Co., London*).—Freed from coating the average weight of each pill is about $\frac{1}{2}$ gr. The formula is Aloin, 0·01 g.; Zinc Phosphide, 0·005 g.; Podophyllum, 0·01 g.; Ext. Damiane, 0·05 g.; Cascarin, 0·05 g.

Cascarets (*Sterling Products Inc., Wheeling, W. Va., U.S.A.*).—Ext. of Cascara Sagrada ("rendered non-bitter"), 0·12; Ext. of Licorice, 0·25; Oil of Aniseed, Oil of Peppermint, Powdered Acacia, Sugar, sufficient quantities.—*Lancet*, i/1924, 256. (As sold in Italy.)

Cassells (Dr.) Brand Instant Relief (*Veno Drug Co. Ltd., Manchester*).—The average weight of each tablet is about 6 gr. The formula is Phenolphthalein, 10·884%; P. Res. Jalapæ, 3·628%; P. Res. Scam., 3·628%; P. Res. Podoph., 0·907%; Sod. Phenol-*p*-Sulphonas, 7·256%; P. Fol. Sennæ, 12·698%; P. Zingib., 17·241%; Sucrose, 31·745%; P. Acaciæ, 6·349%; Ol. Menth. Pip., 0·112%; Ol. Res. Zingib., 0·112%; Mag. Silic. Nat., 5·440%.

Cassells (Dr.) Brand Tablets (*Veno Drug Co. Ltd., Manchester*).—The average weight of each tablet is about 6 gr. The formula is Cal. Hypophos., 15·52%; Man. et Mag. Hypophos., a.a. 0·69%; Sod. Phenol-*p*-sulphonas, 15·42%; Ferri Glycerophos., 0·69%; Cort Cinchonæ, 11·50%; Kolæ Sem., 27·77%; Sabal et Sumbul Rad., a.a. 3·08%; Saccharomyces Cerevisiæ, 3·08%; Cal. Phos., 5·76%; Mag. Silic. Nat., 4·50%; Salicin et Pepsin, a.a. 0·77%; Papayotin, 0·50%; Ol. Anisi, 0·59%; Acaciæ Gum., 5·10%; Ol. Pet. Alb., 0·39%; Gelatin, 0·10%.

Celmetz (formerly **Celmo No. 2**) (*Celmo Ltd., London*).—An analysis showed these tablets to contain Pepsin, about 3 gr. in each tablet, together with Diastase (probably in the form of Malt Extract) and Socotrine Aloes. No evidence was found of any other ingredient.—*Brit. med. J.*, i/1912, 438.

Celmo No. 1.—The proportions of the various constituents were determined as accurately as practicable, and indicated the following formula:—Acetylsalicylic Acid, 35·5; Powdered Charcoal, about 8·0; Malt Extract, dry, 18·0; Magnesium Silicate, 14·5; other Mineral constituents, 2·8; Water, 12·3; Alkaloid, 0·5; Extractive, about 8·0%; Oleo-resin of Capsicum, a trace; Oil of Juniper, a trace.—*Brit. med. J.*, ii/1910, 986.

Chameleon Oil (*The Castle Laboratory, London*).—A mixture prepared by the following formula agreed in physical and chemical properties with the original, except in regard to some minor characters of the Resins. Essential Oils of Mustard, 0·75; Spearmint, 0·45; Pimento, 1·5; Cassia, 1·5; and Camphor, 13·0; Oil of Turpentine, 15·0; Alcohol (90%), 7·3; Strong Solution of Ammonia, 8·0; Resins, 1·6; and Water, to 100. All in parts by measure.—*Brit. med. J.*, ii/1910, 983.

Chrisman Brand Constipation Tablets (*L. M. Chrisman & Co. Ltd. London*).—Calomel, $\frac{1}{2}$ gr.; Pil. Rhei Co., 1 gr.; Pil. Colocynth. Co., 1 gr.; Extract Gentian., 2 gr.; Excipient, $\frac{1}{2}$ gr.

Cicfa Brand Tablets (*Cicfa Co., London*).—Vegetable Charcoal, $\frac{3}{8}$ gr.; Pepsin (1 : 3,000), 1 gr.; Diastase, $\frac{1}{3}$ gr.; Ext. Cascara Sagrada, $\frac{1}{4}$ gr.; Aloin, $\frac{1}{32}$ gr.

Clarkes Brand Blood Mixture (*Lincoln and Midland Counties Drug Co. Ltd., Lincoln*).—Potass. Iod., 1.084%; Sod. Salicyl., 1.304%; Sod. Nuclein 0.200%; Potass. Bicarb., 0.865%; Ammon. Chlorid., 0.652%; Liq. Gent. C., 0.107%; Trichloro-Methane, 0.237%; Sp. Vini. Rect., 0.237%; Sol. Colours 0.498%; Aq. Dist., 94.816%.

Clarkes Brand Salve (*Lincoln and Midland Counties Drug Co. Ltd., Lincoln*).—Zinci Oxid., 10.000%; Ac. Hydroxybenzoic., 1.5%; Thymol, 0.25%; Resin Coloph. Purif., 10.000%; Paraff. Dur., 3.5%; Paraff. Moll. Flav., 74.75%.

Clarkes Brand Skin Lotion (*Lincoln and Midland Counties Drug Co. Ltd., Lincoln*).—Liq. Carb. Det., 10.000%; Sodii Biborat., 2.50%; Ol. Thymi Vulg. 0.05%; Glycerol, 1.50%; Aquæ Dest., 85.95%.

Clarkson's Brand Medicine and Embrocation (*Clarkson, Ryde*).—T. Zingib., 1.250; Tr. Myrrhæ, 1.875; Spt. Camphor, 1.875; Pulv. Capsici 7.000; Pulv. Cocci Cacti, 0.062; Spt. Vini Rect., 50.000; Aq. ad. 100.000.

Clotabs (*Macleans Ltd., London*).—Halibut Liver Oil Concentrate, 8% Base, 32%; Coating, 60%.

Cockles Brand Antibilious Pills (*James Cockle & Co. Ltd., London*).—The average weight of each pill (uncoated) is nearly 2 gr. The formula is Aloes Soc., 17.72%; Aloes Barb., 17.72%; Colocynth, 8.86%; Jalap. Pulv., 8.86%; Pulv. Anthem. Flor., 8.86%; Solazzi, 8.86%; Gamboge, 8.86%; Excipient 20.26%.

Cofluxol (formerly **Baines' Dielectric**) (*Coflux Ltd., London*).—The consists of Liquid Paraffin and is stated to have been treated by a special process "which makes it a thoroughly reliable dielectric; without this process its therapeutic action would be unreliable."

Colchi-Sal (Huxley Brand) Capsules (*Anglo-American Pharmaceutical Co. Ltd., Croydon*).—Each capsule contains $\frac{1}{4}$ mg. ($\frac{1}{250}$ gr.) of Colchicin dissolved in 0.2 g. of Methyl Salicylate (from the *betula lenta*).

Collis Browne's (Dr. J.) Chlorodyne (*J. T. Davenport Ltd., London*).—The poisonous ingredients are now stated to be Ext. Opii Liq. (10% morphine) 1.4%, and Codeine Phosphate, 0.21%.

Congreve's Elixir (*G. T. Congreve Ltd., London*).—(Cough Mixture).—Analysis of the Elixir showed 28.5% by volume of Alcohol together with resinous material similar to the resins of Benzoin, Storax, Tolu or Balsam of Peru; Sugar, about 1%; Alkaloid, under 0.001%.—*Brit. med. J.*, ii/1908, 505.

The carton round the bottle states "Free from poison."

Constipon Laxatives (*Constipon, Glasgow*).—Phenolphthalein, $1\frac{1}{2}$ gr., in chocolate base.

Cornol Brand Corn Remover (*Thompson & Capper Wholesale Ltd. Liverpool*).—Ortho-Oxybenzoic Acid, 11.2%; Chromule Absolute, 1.4%; Collodion Flexile, ad 100.

Cream of Magnesia "Wampole" (*Henry K. Wampole & Co. Ltd., Perth Ontario*).—Magnesium Hydroxide, 32 gr.; Glycerin, 12 m.; Aq. Dest. ad 1 oz.

Crosby's Balsamic Cough Elixir (*Dr. Charles Rooke Ltd., Leeds*).—Oxymel Scillæ, 26.03; Syr. Tolu., 26.03; Syr. Rhæados, 26.03; Chloroform Puri P.B., 0.54; Spt. Vini Rect., 7.04; Ext. Ipecac. Liq. P.B., 0.32; Acid. Acetic Fort., 0.04; Ac. Sulph. Pur., 0.75; Aq. Dest. ad 100.00.

Curicones (*Stephens Matthews & Co. Ltd., London*).—Analysis showed Sulphur, Lactose, Guaiacum Resin (about 10%), Acetylsalicylic Acid, Sodium Benzoate (about 25%), and a powdered vegetable drug resembling *Cimicifuga* Rhizome. Average weight of contents of one capsule is about $2\frac{1}{2}$ gr.—*Brit. med. J.*, i/1915, 992.

Cuticura Ointment (*Potter Drug and Chemical Corp., Boston, U.S.A.; Newbery & Phillips, Ltd., London*).—Hard and Soft Paraffins, slightly perfumed with rose and coloured green.—*Brit. med. J.*, i/1908, 944.

Cuticura Pills (*Potter Drug and Chemical Corp., Boston, U.S.A.; Newbery & Phillips, Ltd., London*).—Aloin, 0.02; Jalapin, 0.02; Podophyllin, 0.003; Capsicin, 0.001.—*Lancet*, i/1924, 256. (As sold in Italy.)

The wrapper, as sold in this country, now bears a declaration that each pill contains "a very small dose of Nux Vomica, equivalent to $\frac{1}{400}$ of grain of Strychnine."

Another formula is Quinine Sulphate, Iron Carbonate, Red Pepper, Nux Vomica, Alkaloids, Iodides, and Aloin.—*J. Amer med. Assoc.*, i/1933., 1624.

Cuticura Resolvent (*Potter Drug and Chemical Corp., Boston, U.S.A., Newbery & Phillips, Ltd., London*).—Potassium Iodide, Sugar and Glucose, Extractive, Alcohol and Water.—*Brit. med. J.*, i/1908, 944.

Cystex Brand Kidney, Bladder and Rheumatism Tablets (Distributors for Great Britain: *G. M. Williams & Co., London*).—Two kinds of tablets are supplied, with grey and brown coatings respectively. The grey tablets contain Hexamethylenamine, $2\frac{1}{2}$ gr.; Thyroid Extract, $1/10$ gr.; Salol, $\frac{1}{2}$ gr.; Benzoic Acid, $\frac{3}{8}$ gr. The brown tablets contain Extract Buchu, $\frac{1}{2}$ gr.; Extract Corn Silk, $\frac{1}{4}$ gr.; Extract Triticum, $\frac{1}{2}$ gr.; Potassium Bicarbonate, 1 gr.; Acetphenetidin, 1 gr.; Sodium Borate, $\frac{1}{2}$ gr.

Daisy Powders (*Daisy Ltd., Horsforth, Leeds*).—Consist of Acetanilide alone, hence exempt from Medicine Stamp Duty. Each powder contains 5 grains—*Brit. med. J.*, i/1906, 27; *Lancet*, ii/1906, 1390; *Chem. & Drugg.*, i/1913, 529.

Dixon stated before the Proprietary Medicine Committee that Acetanilide is a dangerous drug, and that "lots of deaths" had been caused by headache powders containing it. J. Lawson, representing "Daisy," however, pointed out that this is not supported by the Registrar General's returns for the last 10 years, only one death being recorded as caused by headache powders (phenacetin), namely, in 1908.

Statements have been made that there have been numerous deaths in America from use of Acetanilide. "Daisy" is not intended for children.—*Chem. & Drugg.*, i/1913, 529; *Pharm. J.*, i/1913, 472.

Details of the introduction of the Company's "Head Powder."—*Chem. & Drugg.*, i/1913, 529. These consist of Phenacetin alone.

Daisy Brand Tablets (*Daisy Ltd., Horsforth, Leeds*).—Each tablet weighs approximately 6 gr. and contains Trimethyl Xanthine, 1.67%; Piperyl-Piperidine, 0.17%; Acet-Paraphenetidin, 24.98%; Acidum Acetyl Salicylicum, 54.16%; Amylum et Excipients, 19.02%.

Dalby's Carminative (*Barclay & Sons Ltd., London*).—Rhubarb, Magnes. Carb., Glycerin, Sugar, Peppermint Oil, Dill Oil, and a small quantity of Laudanum.—*Lancet*, ii/1903, 1493. The bottle bears a declaration that the preparation contains 0.625% of Tinct. Opii.

Damaroids.—Freed from coating the tablets had an average weight of 3.9 grains. The figures arrived at were Iron Hypophosphite, 14.2%; Quinine Sulphate, 3.4%; Extract (probably Damiana) 50%, Sugar, Talc, 16%.—*Brit. med. J.*, i/1911, 27.

Darley's Toothache Plasters (*Johnson & Johnson Ltd., Slough*).—Pimento, Black Pepper, Cloves, 10% of each, rubber solution, sufficient quantity.—*Lancet*, i/1924, 256. (As sold in Italy.)

Davis' Famous Female Pills.—*Inter alia*, Powdered Savin, $1\frac{1}{2}$ grains in each, with Sulphate of Iron.—*Brit. med. J.*, ii/1907, 1654. The container is not labelled "Poison" so that presumably the pills no longer contain Savin. A mixture made by the same proprietors contains Gossypium.—*ibid*.

D.D.D. Brand Prescription (*D.D.D. Company Ltd., London*).—Ortho Hydroxy Benzoic Acid, 0.739%; Isopropyl-metacresol, 0.092%; Trichlor-tertiary butyl alcohol, 1.109%; Methyl ester of ortho Hydroxy Benzoic Acid, 1.149%; Hydroxy Benzene, 1.849%; Tri Hydroxy Propane, 9.322%; Ethanol, 33.940%; Aqua destillata, to 100%.

Dearborn Ltd.'s Preparations (*Dearborn Ltd., London*).—"Stallax" and "Allacite of Orange" before the P.M.C.E.—*Pharm. J.*, i/1913, 770; *Chem. & Drugg.*, i/1913, 831.

De Roos' (Dr.) Compound Renal Pills (*De Roos, Johnson & Co., London*).—Freed from coating, the average weight of each pill was 4.5 grains. They contained Soap, 34.2%; Sodium Carbonate, 19.7%; a Resin (uncertain, probably Ammoniacum), 3.3%; and a small quantity of vegetable tissue with moisture and extractive. Vegetable tissue could not be identified.—*Brit. med. J.*, ii/1911, 78.

De Witts Brand Kidney and Bladder Pills (*E. C. De Witt & Co. Ltd., Croydon*).—Freed from coating, the average weight of each pill is about 3 grains. The formula is "Meth. Bleu," 2.10%; Pot. Nit., 15.73%; Ext. Casc. Sag., 10.48%; Ext. Uva. Ursi, 10.48%; Pichi, 3.14%; Podoph. Pelt., 10.00%; Ol. Juniperi, 2.10%; Buchu Fol., 2.10%; Excip., *q.s.*

Doan's Brand Backache Kidney Pills (*Foster-McClellan Co., London*).—Freed from coating the average weight of each pill is about 3 grains. The formula is Ext. Uva Ursi, 12·698%; Ext. Buchu, 3·175%; Ext. Gent., 8·333%; Aloin 0·334%; Potass. Nitrat., 12·698%; Ol. Junip. Conc., 1·333%; Ext. Cubeba 3·00%; P. Fol. Buchu, 11·500%; Pulv. Fol. Uva Ursi, 36·000%; Excip., 10·929%.

Doan's Brand Ointment (*Foster-McClellan Co., London*).—P. Zinci Oz Puriss., 13·333%; Hydrarg. Subchlor., 17·778%; Phenol, 1·667%; Paraff. Dur 5·555%; Paraff. Mollis Fl., 61·667%.

Dodd's Kidney Pills (*The Dodds Medicine Co., Leigh-on-Sea*).—A pill containing Cascarella, Jalap, Soap, Potassium Nitrate, Sodium Bicarbonate, Hard Paraffin, Turmeric and Wheat Flour is stated to be practically identical.—*Brit. med. J.*, ii/1906, 1646.

Do-Do Brand Tablets (*International Laboratories Ltd., London*).—(*For asthma*).—Phenylhydroxyisopropylmethylammonium Chloride, 10%; Trimethylxanthine, 15%; Ext. Grindelia Campor., 10%; Dimethylaminophenyl methylisopyrazolone, 30%, to 3½ grains tablet; with Dimethylxanthine Calcium Hydroxybenzoate, 1 gr., and Calcium Gluconate to 5 gr.

Eade's Brand Rheumatic and Gout Pills (*George Eade Ltd., London*).—Each pill weighs about 4½ grains. The formula is Ext. Colchici (*B.P.* '14 25%; Aloe Curacao, 12·5%; Acaciæ G., 6·94%; Guaiaci Res., 1·39%; Sacch Lact., 2·77%; Colchici Corm., 16·67%; Glycyrrh. Rad., 34·73%.

Elliman's Embrocation (*Elliman, Sons & Co. Ltd., Slough*).—Acetic Acid (30%), 180; Oil of Turpentine, 300; Camphor, 20; Egg Yolk, 100; Distilled Water, 400.—*Lancet*, i/1924, 256. (As sold in Italy.)

Embrocine Brand Embrocation (*The Coronette Preparations Co., Ltd London*).—This preparation is stated to be an "Antiseptic Spirit Embrocation consisting of a Compound Distillate of Capsicum, Arnica, Camphor, Menthol, Terebinte, combined with Potassium Oxychinolinsulphonate."

Endrine Nasal Compound (*Petrolagar Laboratories Ltd., London*).—(*For coryza, asthma, hay fever, etc.*)—Ephedrine, 0·75%; Menthol, 0·5%; Camphor, 0·5%; Eucalyptol, 0·5%; Liq. Paraffin, q.s.

Eno's Fruit Salt (*J. C. Eno Ltd., London*).—(*Aperient*).—Sodium Bicarbonate, Tartaric Acid and Citric Acid.—*Lancet*, ii/1903, 1493. Contains no Sodium or Magnesium Sulphate.

Ephazone Tablets (*The Ephazone Co., London*).—(*For asthma*).—Each tablet is stated to contain ½ gr. of Ephedrine Hydrochloride "in combination with 28 other *B.P.* drugs."

Ephedrol Brand Inhalant (*Clay & Abrahams Ltd., Liverpool*).—Ephedrine 1·0; Menthol, 2·0; Camphor, 2·0; Cinnamic Aldehyde, 0·015; Phellandrene 0·0012; Alkannin, 0·05; Methyl Ether Allyl Di Hydroxybenzene, 0·0014; Paraffin. Liq. ad 100·00.

Evan's Antiseptic Throat Pastilles (*Evans Sons, Lescher & Webb Ltd Liverpool*).—Essential Oil of Pine, 0·01; Menthol, 0·002; Chlorate of Potash 0·003; Borax, 0·03; Ext. of Licorice, 0·07; Powdered Acacia and Sugar, a sufficient quantity.—*Lancet*, i/1924, 256. (As sold in Italy.)

Ex-Lax Brand Chocolate Laxative (*Ex-Lax Ltd., Slough*).—Each tablet weighs approximately 20 grains and contains 10% of Phenolphthalein and 90% of Chocolate.

Faivre (Dr.) Brand Cachets (*P. Basset, Paris; P. Basset (London) Ltd London*).—Oxyquinotheine (stated to be a molecular compound of Hydroxy caffeine and quinine), 0·15 g.; Amidopyrine, 0·15 g.; Acetphenetidine, 0·25 g.; Magnesia Calc., 0·1 g.

Famel Brand Syrup (*P. Famel, Paris; Wilcox Jozeau & Co. Ltd., London*).—Purified Creosote, 1·00 g.; Calc. Lactophosph., 0·50 g.; Codeine, 0·025 g.; Alcoolat Aconit. (French Codex), 0·50 g.; Syr. Limonis ad 100·0 g.

Fashing Brand Uric Acid Pills (*Promedico, London*).—Freed from coating the average weight of each pill is approximately 2 grains. The formula is Arnica 7·5; Sumac, 2·5; Jalap, 50·0; Parsley, 10·0; Licor., 30·0.

Fellows Compound Syrup of Hypophosphites (*Fellows Medical Manufacturing Co. Ltd., Montreal*).—Each fluid drachm contains Manganese Hypophosphite, ½ gr.; Potash Hypophosphite, ½ gr.; Soda Hypophosphite, ½ gr.; Iron Hypophosphite, ½ gr.; Lime, ½ gr.; Quinine, 1/20 gr.; Strychnine 1/64 gr.

Fellows Laxative Tablets (*Fellows Medical Manufacturing Co. Ltd Montreal*).—Each tablet contains Extract of Cascara Sagrada, 0·049 g.; Aloin 0·008 g.; Podophyllin, 0·0065 g.

Felsol (*British Felsol Company Ltd., London*).—(*For asthma*).—Phenyl-dimethyl-isopyrazolone, 0·47; Phenyl-dimethyl-iodopyrazolone, 0·03; Anilipyrine β , 0·4; Caffeine, 0·1; Ext. Visc. Alb., 0·01; Ext. Brachycladii, 0·01.

Fennings' Fever Cure (*Alfred Fennings Ltd., Cowes, I. of W.*).—A dilute solution of Nitric Acid flavoured with Peppermint.—*Lancet*, Jan. 10, 1925 (Supplement).

Fennings' Lung Healers (*Alfred Fennings Ltd., Cowes, I. of W.*).—Average weight of one pill was 0·22 grain; chemical analysis and microscopical examination showed presence of Ipecacuanha only. Alkaloid present amounted to 1·8%.—*Brit. med. J.*, ii/1911, 1543.

Fennings' Children's Cooling Powders (*Alfred Fennings, Ltd., Cowes, I. of W.*).—Average weight 3·4 grains. Analysis showed the powder to consist of Potassium Chlorate, 70%, and Powdered Liquorice, 30%.—*Brit. med. J.*, ii/1908, 1022.

Freeman's Chlorodyne (*Freeman's Chlorodyne Ltd., London*).—The poisonous ingredients are stated to be Ext. Opii Liq. (10% morphine, anhydrous), 1·5%; Codeia Phosph., 0·22%; Chloroform, 6%. Other ingredients include Ether, 1·5%, and Proof Spirit, 1·7%.

Freezone Brand Corn Remover (*International Chemical Co. Ltd., London*).—Terebinth. Canadens., 5·5%; Ol. Ricini, 3·5%; Zinc. Chlor., 2%; Acid. Salicyl., 14%; Collodium, 75%.

Fuller Brand Celery Perles (*Lowthers of London Ltd., London*).—Each perle contains Solid Extract prepared from fresh Celery Seed, 1·20 gr.; Solid Extract of Buchu, 0·20 gr.; Phenolphthalein, 0·20 gr.; Solid Ext. Cimicifugæ, 0·10 gr.; Sulphur Sub., 0·40 gr., Sodii Sal., 0·90 gr.

Gabail Brand Elixir Bromo-Valerianate (*Gabail Ltd., London*).—Extract of Valerian (deodorised), 4·00 g.; Acid. Valerianic (deodorised), 1·00 g.; Ammonium Carbonate, 2·50 g.; Strontium Bromide, 4·00 g.; Syrup Aurantii (Fr. Cx.), 100·00 g.; Distilled Water, 100·00 g.

Gabail Brand Syrup Pertussis (*Gabail Ltd., London*).—Ext. Valerian, (deodorised), 2·40 g.; Amm. Valerian (deodorised), 2·00 g.; Potassium Bromide, 2·25 g.; Chloral Hydrate, 2·25 g.; Ext. Grindelia Liq., 1·25; Ext. Polygala Liq. 1·25; Syrup Rubus Idæus, 60 ml.; Aqua Destillata, ad 125 ml.

Gee's Lobelline (*Squire & Co. (Birmingham) Ltd., Birmingham*).—Theriacæ Opt., 38·63; Mellis et Lævulosi a.a. p. aeq. ad 19·31; Lobelia Inflat. Incis B.P., 0·34; Liq. Rhœados, 1·7; Oxytel Scillæ, 4·54; Ext. Glycyrr. Liq., 4·54; Ext. Senegae Liq. U.S.P., 0·22; Ext. Ipecac. Liq. P.B., 0·11; Ext. Pulmonii Liq., 0·22; Ext. Pruni Virg. Liq., 0·9; Ext. Marrubii Liq., 1·81; Pulv. Tragacanth., 0·02; Spt. Vini Rect., 1·42; Æther Sulph., 0·28; Chlorof. Pur., 0·9; Tinct. Capsici, 0·45; Ol. Menth. Pip., 0·05; Ol. Anisi, 0·02; Ol. Menth. Viridæ, 0·02; Ol. Menth. Pulegii, 0·02; Tinct. Quillaia, 0·11; Aqua ad 100·00.

Gelineau (Dr.) Brand Dragées (*Mousnier, Paris; Wilcox, Jozeau & Co., London*).—(*For epilepsy*).—Each dragée contains Kali Brom., 1·00; "Sal. Antim. Arsen.," 0·001; "Sal. Picrotox.," 0·0005.

Germolene Brand Blood Purifier and Tonic (*Veno Drug Co. Ltd. Manchester*).—Dec. Sarzæ Co. Conc., 16·25; Mist Sennæ Co., 37·5; Pot. Iodid., 0·45; Ferri et Ammonii Citras, 2·05; Syrupus, 31·25; Aq. Chlorof. ad 100·00

Germolene Brand Ointment (*Veno Drug Co. Ltd., Manchester*).—Adep. Lanæ Anhyd., 53·2%; Paraffin. Molle., 26·601%; Amylum ex zea Mays, 7·98%; Zinci Oxid., 7·99%; Ethyl *o*-Hydroxybenzoas, 3·011%; Phenyl Hydras, 1·202%; Methyl-Propyl-Phenolhexahydride, 0·012%; Toluene-azo-toluene-azo-B-Naphthol, 0·004%.

Germolets (*Veno Drug Co. Ltd., Manchester*).—Each tablet weighs approximately 6 grains. The formula is Berberis Aquifol., 17·857; Echinac. Angus., 17·857; Cal. Phos., 35·714; Acacia Gum., 7·120; Sucrose, 17·857; Ferri Glycerophos., 1·785; Salicinum, 0·223; Mag. Silic. Nat., 1·567; Ol. Aurant T'pless, 0·020.

Gloria Pills (*John A. Smith, London*).—The following was indicated:—Extract of Cascara, 0·3; Ext. Soc. Aloes, 0·5; Jalap Resin, 0·07 grain; Flour and Excipient q.s. in one pill.—*Brit. med. J.*, ii/1908, 1111; see also *Lancet*, ii/1903, 1493.

Gloria Tonic (*John A. Smith, London*).—(*Gout and rheumatism tablets*).—The following formula was indicated; Potassium Iodide, 1·8; Guaiacum Resin,

0.8; Ext. Liquorice, 1.0; Resinoid (Phytolaccin?), 0.9; Powdered Liquorice, 1.7; Rice Starch, 2.0; Talc and Kaolin, 2.1 gr.—*Brit. med. J.*, ii/1908, 1111.

Glykaline (*Leath & Ross Ltd., London*).—(For coughs, colds, catarrhs, etc.)—Analysis showed the liquid to contain 35% of Alcohol and 0.15% of solid matter consisting of Potassium Iodide and partly of organic matter. Each dose would contain 1/350 gr. of Potassium Iodide, with a trace of organic matter which may be derived from some drug.—*Brit. med. J.*, ii/1911, 1544.

Golden Fire (*W. H. Box, Plymouth*).—The following is the formula given by the analyst:—Oil of Amber, 0.16; Oil of Rosemary, 0.16; Oil of Eucalyptus, 0.32; Essential Oil of Camphor, 1.3; Sodium Chloride, 6.4; Glacial Acetic Acid, 6.4; Alcohol, 1.0; and traces of decoction of Capsicum, Barley and Lobelia.—*Brit. med. J.*, ii/1910, 987.

Grains de Vals (*H. Nogues, Paris*).—Each pill contains Erepsine, 0.010 g.; Ext. bilia, 0.020 g.; Podophyllina, 0.010 g.; Enterokinase, 0.010 g.; Cascara Sagrada, 0.025 g.; Rhamnus Frangula, 0.025 g.

Grasshopper Brand Ointment (*Grasshopper Ltd., London*).—Resina, 31.68; Cera Flav., 7.94; Ext. Pini Larix, 23.74; Ol. Olivæ, 15.84; Par. Molle Alb., 19.81; Cupri Acetas, 0.99.

Grasshopper Brand Pills (*Grasshopper Ltd., London*).—Freed from coating the average weight of each pill is about 1 gr. The formula is Aloes Barb., 25.0; Jalap. Pulv., 37.5; Ext. Taraxaci, 12.5; Ext. Anthemidis, 12.5.

Gripe Water Brand Carminative (*W. Woodward Ltd., London*).—Ol. Anethi, 2 m.; Sodii Bicarbonas, 20 gr.; Spiritus Rectificatus, 110 m.; Syrupus Simp., 9½ fl. drm.; Aqua Dist., 3 fl. oz.

Guy's Brand Tonic (*Guy's Tonic Ltd., London*).—Gentianæ Luteæ Radix, 0.178; Citri Aurantii Cortex, 0.067; Elettariæ Minusculæ Semina, 0.022; Dactylopius Coccus, 0.178; Spiritus Chloroformi, 3.58; Acidum Phosphoricum, 0.033; Acidum Glycerophosphoricum, 0.033; Acidum Nitricum, 0.123; Acidum Muriaticum, 0.164; Aqua, q.s.

Hair's (Dr.) Asthma Cure (*Dr. Hair's Asthma Cure Ltd., London*).—A fluid containing 5.6% Potassium Iodide, Tar Water and some Wine.—*Lancet*, ii/1903, 1493; *Brit. med. J.*, i/1907, 879.

Halmagon Brand Tablets (*Tonicity Laboratories Ltd., London*).—("For use as a daily ration to promote and maintain maximum metabolic activity.")—The formula is Magnesii Chloridi, 0.395 g.; Magnesii Bromidi, 0.0133 g.; Magnesii Iodidi, 0.000067 g.; Magnesii Fluoridi, 0.0006 g.; Excipient, q.s. = 0.45 g.

Himrod's Asthma Cure (*Himrod Mfg. Co., Hoboken, N.J., U.S.A.*).—Bears a declaration that it contains Hyoscyamine, 0.05%, Atropine, 0.09%, and Lobeline, 0.03%—the alkaloids "occur as such in the natural medicinal principles which are employed in the manufacture of this therapeutic product."

Holloway Brand Ointment (*Holloway's Pills Ltd., Watford*).—Adeps Lanæ Anhy., 14.63; Petrolatum Liq. U.S.P., 9.70; Terebinth ex Pinus Larix, 29.26; Cera Flavum, 12.19; Cetaceum Opt., 14.63; Ol. Theobromatis, 17.07; Amyl-m-Cresol, 0.02; Ol. Picis Rect., 2.00; Phenyl Hydroxidum, 0.50.

Holloway's Pills (*Holloway's Pills Ltd., Watford*).—The pills had an average weight of 1.4 gr. Examination showed the presence of Aloes (Barbadoes) or a preparation of Aloes, Powdered Ginger and Soap.—*Brit. med. J.*, i/1911, 1326.

Holdroyd's Gravel Pills (*J. Holdroyd Ltd., Cleckheaton, Yorks.*).—Freed from coating the average weight of each pill was 4.3 gr. From analysis the following formula was arrived at:—Soap, 40; Dried Sodium Carbonate, 20; Powdered Rhubarb, 20; Oil of Anise, 10; Syrup, 10.—*Brit. med. J.*, ii/1911, 77.

Hood's Medicine or Hood's Sarsaparilla (*C. I. Hood Co. Inc., New York*).—Dose, ½ to 2 teaspoonfuls. Analysis indicated 19% by volume of Alcohol and 7½ gr. of Potassium Iodide in the ounce, the amount of Sarsaparilla being small.—*Brit. med. J.*, ii/1907, 531.

According to the carton the preparation contains Sarsaparilla, Mandrake, Yellow Dock, Gentian, Wintergreen, Uva Ursi, Juniper Berries, Dandelion, Blue Flag, Stillingia, Senna, Wild Cherry, Bitter Orange Peel, and Guaiac.

Hood's Vegetable Pills (*C. I. Hood Co. Inc., New York*).—Freed from coating the average weight of each pill was ½ gr. Examination showed Aloes (Barbadoes) or a preparation of Aloes (probably Aloin), Ginger, Capsicum, Colocynth, Soap and probably a little Jalap.—*Brit. med. J.*, i/1911, 1327.

Hooper's, Dr. John, Female Pills (*Dr. John Hooper's Female Pills Co. Ltd., Reading*).—Analysis showed Iron Sulphate, Aloes, Jalap, Canella, Senna and Oil of Pennyroyal.—*Brit. med. J.*, ii/1907, 1653.

Hughes' Blood Pills (*J. B. Hughes, Penarth, Cardiff*).—Contain Aloes, Jalap, etc.—*Brit. med. J.*, ii/1907, 532.

Hyomee (Booth's), formerly **Hyomei** (*R. T. Booth's Hyomee Ltd., London*).—From examination it was concluded that Alcohol and Liquid Paraffin formed each about 10% of the whole, Eucalyptus Oil (and possibly other oils) appears to form the remaining 80%—a small proportion of a mixture containing Wood Tar and Creosote was also indicated.—*Brit. med. J.*, ii/1911, 1544.

Idozan Brand Colloidal Iron (*Serpens, Copenhagen; Coates & Cooper, London*).—Colloidal Iron Solution, 83%; Pure Alcohol, 6%; Sugar, 10%; Flavouring (Æther acetic, Oleum limonis, Oleum aurant.), 1%.

Injectio Brou (*Charles Favrot, Paris*).—Label on the carton gives the following:—"Formule pour 100 cm.³—Aceta Plumbi, 0·60; Sulfas Zinci crist., 0·30; Opium, 0·01; Color. vegetal croc. sativa-catechu, 0·01; Aqua stillata, 99·08."

Inotyol Brand Ointment (*Dr. Debat, Paris; Wilcox Jozeau & Co. Ltd., London*).—Ammon Sulficthyol, 1·477; Ext. Hamamel. dist., 0·984; Zinc Oxide, 14·763; Titanium Dioxide, 4·921; Titanic Hydroxide, 0·984; Sodium borate, 0·099; Vasolanolina, q.s. for 100·00.

Iodex Brand Liquid Iodine (*Menley and James Ltd., London*).—Resublimed iodine, 2%, in pure vegetable oil.

Iodex Brand Ointment (*Menley and James Ltd., London*).—Resublimed iodine, 4%, in a neutral parogen, petrolatum base.

Iodia (*Battle & Co., St. Louis, U.S.A.*).—Stated to be a combination of active principles obtained from the green roots of stillingia, helonias, saxifraga, and menispermum, with aromatics; each fluid drachm contains also 2½ gr. of "iod-potas" and 1½ gr. of "phos-iron." The preparation contains 30% of alcohol. Liq. Ext. of Queen's Root, False Unicorn Root, Pimpinella, Saxifrage, Menispermum, equal parts to 125, Pot. Iodide 7·5; Iron Pyrophosphate, 5.—*Lancet*, i/1924, 256. (As sold in Italy.)

Ionized Iodine (Molson Brand) (*The Molson Ionized Iodine Co., Ltd., Maidstone*).—The *Surgical Solution* is stated to be a 1 in 115 solution in 10% aqueous solution of "Propanetriol" of Iodine, 7·91 parts; Chlorine, 10·04 parts; Potassium, 2·89 parts; Sodium, 1·16 parts; Magnesium, 0·76 part; Ammonium, 1·02 parts; Hydrogen, 0·05 part; Salicylic Acid, 2·00 parts; Chloro-Phenols, 2·00 parts. The *Medical Solution* appears to be of similar composition.

Iron Jelloids (*The Iron Jelloid Co. Ltd., Watford*).—Nos. 1, 2 and 3 are prepared from the following formula:—Ferri Protocarbonas, circa 33·333; Glucosum, 43·266; Benzosulphinidum, 0·017; Gelatinum, 9·833; Methyl-protocatechuic Aldehyde, 0·033; Aqua Pura, 13·518. The approximate weight of each "Jelloid" is No. 1 (for children), 3 gr.; No. 2 (for adults), 6 gr.; No. 3 (extra strong), 9 gr. No. 2a Jelloids (containing Quinine) each weigh about 6 gr. and contain the above ingredients with 3·845% of Quininæ Sulphas.

Iron-Ox Brand Tonic Tablets (*Pharmacol Laboratories Ltd., London*).—Manganese Citrate, ⅓ gr.; Hæmoglobin, 1/12 gr.; Ext. Gentian., 1/12 gr.; Ext. Cascara Sagrada, 1/9 gr.; Aloin, 1/36 gr.; Oleoresin Capsicum, 1/100 gr.; Ferri Co. Mass., to 1 gr.

Irvona Brand Tonic Flesh Builder (*London and Colonial Export Co. Ltd., London*).—Ferri Hypophos., 1 gr.; Calcii Hypophos., 1½ gr.; Sodii Hypophos., ½ gr.; Hæmoglobin, ⅓ gr.; Pepsin, ½ gr.; Diastase, ⅓ gr.; Leptandrin, ⅓ gr.

Johnson's (Mrs.) American Soothing Syrup (*Barclay & Sons Ltd., London*).—Analysis showed in 100 by measure Sodium Chloride, 5·66; Hydrochloric Acid (*B.P.*), 2·33 by measure; Reducing Sugars, calculated as Glucose, 66·6; extractive, colouring matter, etc., about 5·0. The Reducing Sugars appeared to be present in the form of Honey, representing about 85 parts of this.—*Brit. med. J.*, i/1912, 683.

The proprietors point out that the preparation does not contain Hydrochloric Acid (*Secret Remedies* and *Brit. med. J.* state as above), but a third of it is lemon juice. Discussion in the *P.M.C.E., Chem. & Drugg.*, ii/1912, 23; see also Parry, *Chem. & Drugg.*, i/1913, 563.

Juvigold Brand Tonic Life Elixir (*The Middlesex Laboratory of Glandular Research Ltd., London*).—Colloidal Gold Sol 0·0005%, Colloidal Palladium Sol 0·0005%, Colloidal Platinum Sol 0·0005%, of each 1·000%; Concentrated Extract of Brain Sub., Concentrated Extract of Spinal Cord Sub., Concentrated Extract of Heart Sub., and Concentrated Extract of Lung Sub., of each, 0·125%; Lipoid Iron-Phosphorus, 0·458%; Proteinic Iodine, 0·115%; Calcium (Lipoid), 0·458%; Isotonic Sol. Lævulosum, 12·000%; Tri-hydroxypropane, 5·000%; Dextrosium (Aromatic) 20·000%, 78·469%.

Kalzana Brand Calcium Sodium Lactate Tablets (*J. A. Wulfinberg Berlin; Therapeutic Products Ltd., London*).—Each tablet weighs about 20 gr. the formula being Calcium Lactate, 18.5%; Sodium Lactate, 18.5%; Saccharum Purificatum, 37.0%; Saccharum Lactis, 10.0%; Talcum, 4.500%; Tartaric Acid, 0.485%; Peppermint Oil, 0.010%; Menthol, 0.005%; Zea Mays Pulv. 11.0%.

Kaputine (*The General Kaputine Syndicate, Ltd., Manchester*).—(For headache and neuralgia).—Contains Antifebrin, 6.3 gr. in each with Sugar 0.21 gr., and coloured with Ferric Oxide, 0.05 gr.—*Lancet*, ii/1903, 1493; *Brit. med. J.*, ii/1906, 28.

Karmoid Brand Tablets (*International Laboratories Ltd., London*).—The formula is stated to be "Dihydroxy-phthalophenone, 1.75% gr." Freed from coating each tablet weighs about 4½ gr.

Karsote Brand Inhalant (*E. Griffiths Hughes Ltd., Manchester*).—Contains in 1000 parts of a spirituous solution the following:—Ol. Absinth., 0.5; Ac. Cinnam., 1; Benzyl Acet., 0.5; Benzyl Alc., 5.0; Borneol, 0.5; Ol. Cassia, 7.5; Ol. Cedri Lig., 2.5; Cinnam. Aldehyde, 7.5; Camphora, 35; Cinnam. Alc., 1.0; Ol. Cinnam., 0.5; Cineol, 85; Ol. Citronel., 25; Ol. Eucalypt., 95; Gerianol., 2.5; Ol. Gram. Cit., 2.0; Limonene, 2.0; Linalol, 0.5; Menthol, 35; Methyl ortho-oxy-benzoate, 75; Phellandrene, 12; Ol. Thymi Rub., 2.5.

Kay Brand Compound Essence of Linseed or Linseed Compound (*Kay Brothers Ltd., Stockport*).—Ol. Anisi, 0.1; R. Senegæ, 0.2; R. Scillæ, 4; S. Lini, 4; Mel, 5; R. Ipec., 0.01; Ac. Acet., 3.3; Picrasmin, 0.001; S.V.R., 0.46; Trichlormethane, 2.3; Methyl Protocatechuate, 0.001; Ethyl Formate, 0.01; Diethyl Ox., 1.2; Syr. Tol. ad 100.

Kay Brand Mountain Flax Pills (*Kay Brothers Ltd., Stockport*).—S. Card. 3.125; Pod., 9.375; Myrrh, 9.375; Rhei, 12.5; Aloe, 12.5; Ex. Gent., 6.25; Ex. Hyos., 6.25; Ex. Lin. Cath., 6.25; Sap., 7.812; Excip. ad 100.

Kay Brand Tic Pills (*Kay Brothers Ltd., Stockport*).—Freed from coating each pill weighs about 3 gr. The formula is Quin. S., 3.846; Cinch. Mur., 19.23; Ferri S. Ex., 23; Ex. Col. C., 23; Ex. Conii, 23; Excip. ad 100.

Keatings Pectoral Lozenges (*T. Keating Ltd. Billingshurst, Sussex*).—Corresponded to Morphine, 0.007 gr.; Ipecacuanha, 0.07 gr.; Extract of Liquorice, 2.1 gr.; Sugar, 13 gr. in one lozenge.—*Brit. med. J.*, ii/1908, 1699.

"Keene's One Night" Cold Cure (*John Pepper & Co. Ltd., London*).—Ingredients found were Cinchonidine Sulphate, 0.21 gr.; Acetanilide, 0.32 gr.; Calcium Carbonate, 0.25 gr.; Starch, 0.34 gr.; Extractive and Excipient, 0.87 gr. (all figures approximate).—*Brit. med. J.*, ii/1908, 1286.

Kephaldol Brand Tablets (*Kephaldol Laboratories Ltd., London*).—Acetphenetidin, 2.15 gr.; Sodium Salicylate, 1.75 gr.; Quinine 0.45 gr.; Caffeine 0.25 gr.; Salicylic Acid, 0.15 gr.; Citric Acid, 0.25 gr.; Amylum q.s.

Kepler Solution of Cod-Liver Oil in Malt Extract (*Burroughs Wellcome and Co., London*).—Analysis showed Oil, 17.4%; Reducible Sugar (as Maltose), 42.5; Protein 3.4, Diastatic Power 3.—*Brit. med. J.*, i/1910, 30.

Ker-Nak Pills (*The Kernak Natural Remedy Ltd., Leeds*).—Freed from coating the average weight of each pill was 1½ gr. Examination indicated Aloe a little Soap, a very little Oleoresin of Capsicum, and a little vegetable tissue resembling Marshmallow root.—*Brit. med. J.*, i/1911, 1327.

Kest Brand Compound Epsom Salts Tablets (*Kest Ltd., London*).—Each tablet contains 4½ gr. of Mag. Sulph. and ¾ gr. of Phenolphthalein. Compound Glauber Salts tablets are also prepared.

Kilmer's (Dr.) Indian Cough Cure (*Dr. Kilmer & Co., London*).—Contains *inter alia* (see ref.) 0.5% Oil of Pumilio Pine. No alkaloid.—*Brit. med. J.* ii/1908, 1698.

Kitano Brand Ointment (*The Kitano Co. Ltd., London*).—(For eczema, rashes, acne, hæmorrhoids, etc.).—Ammon. Sulpho-ichthyolas, 2; Zinci Hydroxy carb., 6; Adeps Lanae, 6; Flores Zinci, 24; Lin. Calcis, 66.

Ki-Uma Brand Ointment (*Ki-uma Ltd., Bath*).—Salicylic ester Dihydroxy ethane, 15%; Cetaceum, 3.5%; Ol. Eucalypti Glob., 1.5%; Ol. Bassiæ Parkii, 80%; Rad. Anchusiæ, q.s.

K.L.X. Brand Tablets (*Michael Hart & Co. Ltd., London*).—(For dysmenorrhæa).—Cortex Cinnamomi, 0.05 g.; Folia Matico, 0.05 g.; Herk. Capsellæ, 0.05 g.; Valeriana Officinalis, 0.05 g.; Potassium Iodide, 0.30 g.

Koko (*Koko-Maricopas Co. Ltd., London*).—Borax, 1.4; Glycerin, 1.0; Formaldehyde Solution (40%), 0.1; Perfume, a trace; Alcohol, 3; Water to 10 by volume.—*Brit. med. J.*, i/1910, 151.

Kolynos Dental Cream (*Kolynos Incorporated, London*).—Calcium Carbonate 21; Soap, 25.5; Thymol, 0.25; Benzoic Acid, 0.3; Saccharin, 0.5; Eucalyptus Oil, 1.75; Peppermint Oil, 1.9; Glycerin, 27; S.V.R., 21.8.—Stated by the makers.

Kruschen Salts (*E. Griffiths Hughes Ltd., Manchester*).—Stated to contain Soda Sulph., Soda Chlorid., Magnes. Sulph., Potas. Sulph., Potas. Chlorid., Ac. Cit.

Lactopeptine Brand Powder (*Beechams Pills Ltd., St. Helens*).—Lac Siccatus, 21.04; Acidum Lacticum B.P., 1.39; Acidum Hydrochlor. B.P., 0.52; Sodii Saccharinas, 0.26; Acidum Citricum, 0.83; Acidum Phosphoricum, 1.49; Essentia, 1.61; Pepsinum, 19.48; Pancreatinum, 8.37; Lactin, 30.47; Diastasum, 5.59; Excipients, *q.s.*

Lamplough's Pyretic Saline (*Aperient*).—(*H. S. Lamplough Ltd., London*).—Citric Acid, Potassium and Sodium Bicarbonates.—*Lancet*, ii/1903, 1493.

Lane's (Dr.) Catarrh Cure (*O. Phelps Brown, Huddersfield*).—Analysis showed Phenol, 0.4; Sodium Chloride, 3.3; Water to 100.—*Brit. med. J.*, ii/1908, 1285.

Langdale's Cinnamon Tablets (*E. T. Langdale, London*).—Oil of Cinnamon, 0.25; Powdered Acacia and Sugar, sufficient quantity, coloured with Carmine.—*Lancet*, i/1924, 256. (As sold in Italy.)

Langdale's Essence of Cinnamon (*E. T. Langdale, London*).—Oil of Cinnamon, 0.30; Tincture of Cinnamon, 30; Alcohol (90%) 54.—*Lancet*, i/1924, 256. (As sold in Italy.)

Laxative Bromo-Quinine Tablets (*Paris Medicine Company, St. Louis*).—The ingredients disclosed are, in each tablet, 1 gr. of Acetanilide, 1/50 gr. of Belladonna and 1/16 gr. Extract of Henbane Leaves.

Licoricine Brand Remedy (*Mandall & Co. Ltd., Newcastle-on-Tyne*).—(*For coughs, colds, asthma, whooping cough, etc.*)—Sucrose, 8.48; "Glycyrra," 2.73; Acetum Scillæ, 4.17; Trihydroxypropane, 1.82; Hydroxy-ethane, 0.728; Trichlormethane, 0.0015; "Camphire," 0.004; "Benzoyl Hydrase," 0.0057; Anisi, 0.006; Mucilage Acacia, *q.s.*

Lilly's (Nurse) Female Pills (*Page Woodcock Ltd., London*).—Freed from coating, the average weight of each pill was 1.9 gr. They contain Exsiccated Sulphate of Iron, 12%; Cinchonine Sulphate, 3.3%; Powdered Capsicum, about 30%; Socotrine Aloes, a little Powdered Ginger and Pennyroyal.—*Brit. med. J.*, i/1911, 36.

Liquifruta (*The Liquifruta Laboratories, London*).—(*A consumption cure*).—Analysis showed Oil of Peppermint, Onion or Garlic Oil and Alkaloids, of each traces; Potassium Bitartrate, 0.4; Glucose, 34.4; Cane Sugar, 2.28; Mucilage, Tannin, Extractive, etc., and Water, to 100.—*Brit. med. J.*, ii/1909, 1419.

Listerine Brand Antiseptic (*Lambert Pharmacal Company, London*).—Thyme, Eucalyptus, Baptisia, Gaultheria and Mentha, of each 1 part; Boric and Benzoic Acids, 29 parts; Ethyl Alcohol, 250 parts; Water, to 1000 parts.

Lockyer's Sulphur Hair Restorer.—(*John Pepper & Co., London*).—Precipitated Sulphur, 1.3%; Lead Acetate, 1.6%; Lead Sulphate, 0.4%; Glycerin, 9.6%; Rose Water, to 100 by volume.—*Brit. med. J.*, i/1910, 151.

Locock's Pulmonic Wafers (*Da Silva & Co., London*).—Lactucarium, Ipecacuanha and Squills.—Murrell. The preparation is stated to contain "2% Ipecac."

Mackenzie Brand Smelling Bottle (*Dr. Mackenzie's Laboratories, Reading*).—(*For catarrh*).—Ammon. Hydrox., 60%; Phenol, 10%; Eucalyptol, 2%; Glyceryl Hydrate, 0.2%; Potass. Oleate, 1%; Absorbent, 26.8%.

Mackenzie One Day Cold Cure (*Mackenzie Medicine Co. Ltd., London*).—Camphor, ½ gr.; Quinine Sulph., ½ gr.; Acetanilid., 1 gr.; Podophyllin, 1/40 gr.; Aloin, 1/32 gr.

Maclean's Brand Rheumatic Rub (*Macleans Ltd., London*).—Pot. Stearate, 10.32; Sod. Oleate, 1.76; Stearic Acid, 9.0; Methyl Salicylate, 22.0; Camphor, 7.7; Menthol, 3.0; Eucalyptol, 4.1; Ol. Succini, 3.9; Terebinth Emulsion (8%) to 100.

McCall Brand Indigestion Capsules (*The Clinical Laboratories Co., Cleveland, Ohio; Tibo Products (International) Ltd., London*).—The average weight of the contents of a capsule is about 3½ gr. The formula is Bismuth Oxide Hydrate, 5%; Powd. Calumba, 20%; Powd. Canella, 5%; Powd. Socotrine Aloe, 10%; Powd. Rhubarb, 10%; Powd. Jamaica Ginger, 5%; Powd. Mag. Carbonate, 15%; Powd. Charcoal, 5%; Sodium Bicarbonate, 25%.

Magnolax Brand Emulsion (*Henry K. Wampole & Co. Ltd., Perth, Ontario; Newbery's Distributing Depot, London*).—Each fluid ounce contains Magnesium Hydroxide, 24 gr.; Liquid Paraffin, 120 m.; Glycerin, 48 m.; Vanillin, 1/25 gr. Distilled Water, *q.s.*

Man Zan Brand Pile Remedy (*E. C. De Witt & Co. Ltd., Croydon*).—Benzocaine, 0.369%; Tannic Acid, 0.738%; Phenol 1.905%; Paraffin. Liq. 1.106%; Paraffin Molle, *q.s.* to 100%.

Marmola Brand Tablets (*General Distributing Agency, London*).—Each tablet contains Ext. Fucus Vesic., 1 gr.; Thyroideum Sic., $\frac{3}{4}$ gr.; Ext. Phytolacea, $\frac{1}{2}$ gr.; Ext. Cascar. Sag., $\frac{1}{4}$ gr.; Calc. Carb. Prec., 3 gr.; Phenolphthalein, $\frac{1}{4}$ gr. Oleoresin "Zinziber," 16/1000 m.; Mixt. a.a. Ol. Anisi, Ol. Sassafras and Methy Salicylas, $\frac{1}{4}$ m.; Sucrose, *q.s.*

Marshall's Cigarettes (*James B. Horner Inc., New York*).—Lobelia inflata, 20; Datura stramonium, 55; Cubeb Fruit, 20; Potassium Nitrate.—*Lancet*, i/1924, 256. (As sold in Italy.)

Martin's Apiol and Steel Pills (*Martin, Southampton*).—1½ gr. of Aloes in each with, *inter alia*, Reduced Iron and Apiol, each 1/10 gr.—*Brit. med. J.*, ii/1907, 1655.

Medilax Brand Laxative Pellets (*Savory & Moore Ltd.; Distributors: Pharmaceutical Products Ltd., London*).—Freed from coating the average weight of each pellet is 2½ gr. The formula is Podoph. (Peltatum) Res., 0.125 gr.; Ext. Pulp. Citrull Colocyn Comp., 0.25 gr.; Curaçoa Aloes, 0.50 gr.; Res. Convolv. Scammon. Rad., 0.125 gr.; P. Sap. Dur., 0.062 gr.; "Aperione," 0.25 gr.; Oleores Zingib., 0.062 gr.

Mentex Brand Embrocation and Inhalant (*Foster-McClellan Co., London*).—Ol. Camph. Ess., 3.261%; Ol. Pini Abiet., 2.447%; Ol. Pini Pumil., 0.394%; Methyl Salicyl., 5.369%; Camphor, 1.812%; Ol. Eucalypt., 0.415%; Iodine 0.076%; Paraff. Dur., 7.839%; Menthol, 0.950%; Paraff. Moll. Alb., 61.760%; Adeps Lanæ Anh., 15.202%; Ac. Benzoic., 0.475%.

Mentholatum Brand Balm (*The Mentholatum Co. Ltd., Slough*).—Ac. Boric Pulv., 3; Menthol, 0.5; Flor. Camph., 3; Ol. Eucalypt., 0.2; Ol. Pini Pum., 0.2; Ol. Gaultheriæ, 0.2; Paraff. Moll. Flav., 30.

Mexican Hair Renewer (*Anglo-American Drug Co. Ltd.; T. Christy & Co., London*).—Precipitated Sulphur, 1.4%; Lead Acetate, 0.1% (one sample examined contained 0.97%); Glycerin, 19.0% Rose Water, to 100 by volume.—*Brit. med. J.*, i/1910, 512.

Milk of Magnesia (Phillips) (*Proprietary Agencies Ltd., London*).—A fluid ounce yields from 32 to 40 gr. of Magnesium Hydroxide, Mg(OH)₂.

Milk of Magnesia Brand Tablets (*Proprietary Agencies Ltd., London*).—Magnes. Hydrox., 53.3%; Saccharum, 33.25%; Amylum, 13.3%; Ol. Menth. Pip., 0.15%. Each tablet is stated to contain the equivalent of one teaspoonful of Milk of Magnesia brand of magnesium hydroxide in concentrated form.

Milton Brand Antiseptic Fluid (*Milton Proprietary Ltd., London*).—Sodium Hypochlorite, 1.01%; Sodium Chloride, 16.80%; Sodium Chlorate, 0.50%; Sodium Sulphate, 0.14%; Sodium Carbonate, 0.20%; Calcium Chloride, 0.08%; Magnesium, a trace; Water, 81.27%.

Milton Brand Antiseptic Ointment (*Milton Proprietary Ltd., London*).—Milton Antiseptic Fluid, 13.80%; T. Sulph. Dichloramid, 0.88%; Mag. Hyd., 0.60%; Calc. Carb., 7.00%; Paraff. Moll., 76.22%; Paraff. Durum., 1.50%

Miol (*Willows, Francis, Butler & Thompson Ltd., London*).—Analysis showed it to contain Oil, 22.4%; Reducing Sugars (as Maltose), 41.3%; Diastatic power, 2.—*Brit. med. J.*, i/1910, 30.

M.O. Brand Magnesia Oil (*Musterole Fire Products Co. Ltd., London*).—Magnesia, 4.0; Emulsion of Petroleum, 96.0.

Moorland Brand Tablets (*W. B. Cartwright Ltd., Rawdon, Leeds*).—Each tablet weighs about 20 gr., the formula being Magnesii Carbonas Ponderosus, 4.8 parts; Pepsinum, 0.075 parts; Calcii Carbonas Præcipitatus, 32 parts; Natrii Bicarbonas, 3.60 parts; Pancreatinum, 0.05 parts; Bismuthi Carbonas, 0.9 parts; Magnesii Silicas Hydras, 2.56 parts; Acaciæ Gummi, 3.2 parts; Methenyl Trichloride, 1.36 parts; Diethyl Ether, 0.4 parts; Saccharum Album, 46.24 parts; Capsicini, 0.005 parts; Oleum Cardamomi, 0.04 parts; Oleum Lavandulæ, 0.02 parts; Oleum Rosæ, 0.01 parts.

Morison's Pills (*Morison & Co. Ltd., London*).—(For obesity.)—Aloes Jalap Resin, Extract of Colocynth, Gamboge, Rhubarb, a.a. 1 g.; and Myrrh 2 g., to make 50 pills. Historical note,—*Pharm. J.*, ii/1922, 381. See also 18th Edn., Vol. II, p. 574.

Mothersill's Seasick Remedy (*Mothersil Remedy Co. Ltd., London*).—Contents of capsules, a pink and brown powder, gave the following result on analysis:—Pink powder.—Lactose, 33.3%; Caffeine, 8.2%; Stearic Acid, 18.0%; Chlorbutol, 40.1%; colouring matter, a trace. Brown powder.—Powdered Cinnamon, 29.4%; Caffeine, 8.4%; Stearic Acid, 17.4%; Chlorbutol, 44.5%; Stearic Acid is probably added as a lubricant to assist in filling the capsules, though the amount is large for the purpose.—*Brit. med. J.*, ii/1910, 1928.

Mother Seigel's Syrup. (*A. J. White Ltd., London*).—A Government chemist, acting upon instructions from the House of Commons Committee on Patent Medicines, 1914, found:—

Organic Ingredients.—The proportion of sugars represents about 40% of Treacle. In addition to the sugars the organic ingredients were found to include:

Essential Oil having an odour of Sassafras, a small quantity; Starch, a small quantity; Acetic Acid, 0.66%; Capsicum, equivalent to about 1% of Tincture of Capsicum B.P.; Aloes, about 1%; Other vegetable extractive substances (after deducting 1.4% of extractives due to Treacle), 7.8%.

Mineral Ingredients consisted of Borax with small quantities of chlorides, sulphates and phosphates such as occur in the ashes of vegetable substances:

Total Boric Acid, 2.12% (equivalent to 3.36% of crystallised borax). Total chlorides, 1.51% (calculated as hydrogen chloride).

Acids.—The volatile acid consisted mainly of acetic acid with a little boric acid. The total free acid of the sample in terms of hydrochloric acid is 1.12%, equivalent to 10.6% of the B.P. Dilute Hydrochloric Acid.

The proportion of free acid, other than acetic acid, would correspond with 0.72% of hydrochloric acid, equivalent to 6.8% of the "diluted hydrochloric acid" of the *Pharmacopœia*. Very little of this hydrochloric acid, however, would be actually present in the "free condition."—*Lancet* Supp. on "Sale of Patent Medicines," Jan. 10, 1925, 11.

Previous information, *Edn. XVII*, Vol. II, p. 577.

Natex Reducing Food (*Natex Food No. 5*).—(*Modern Health Products Ltd., London*).—Is stated to contain "Celery, Cranberries, Dulse, Irish Moss, Rhubarb (not Turkey) and Spinach."

Nemolin Brand Pile Ointment (*Saltrates Ltd.; International Chemical Co. Ltd., London*).—Zinc Ox., 19%; Amylum, 18%; Glycerinum, 2%; Hamamelis, 15%; Paraffinum, 46%.

Nervlettes, Coleman's (*N. & R. Manufacturing Co. Ltd., Norwich*).—Phosphorus, 0.005 gr., and Quinine Sulphate, 0.07 gr., with vegetable matter, 0.3 gr., were determined.—*Brit. med. J.*, i/1909, 32.

Neuraline (*Leath & Ross, London*).—(For external use in neuralgia, etc.)—Is stated on the label to contain 60% of Tinct. Acon. Rad. (10%). Aconite, Chloroform and Rose Water.—Murrell (11th Edn.).

New Skin (*Agents: J. E. Garratt & Sons Ltd., London*).—Pyroxylin, 5; Acetone, 50; Benzol, 20; Amyl Acetate, 25.—*Lancet*, i/1924, 256. (As sold in Italy.)

Norton's Camomile Pills (*Norton's Ltd., Leigh-on-Sea*).—Aloes, Gentian and Chamomile Oil.—Murrell.

According to *Lancet* i/1924, 256:—Cape Aloes, 0.03; Ext. of Gentian, 0.12; Oil of Chamomile, 0.02; Powdered Gentian, a sufficient quantity. (As sold in Italy.)

Nestroline Brand Nasal Remedy (*Matthews Laboratories, Ltd., Bristol*).—Vegetable Stearine, 5.970; Boric Acid, 3.981; Cineol, 0.244; Petrolatum, 87.562; Menthol, 0.313; Phenol, 1.656; Geranium Oil, 0.274%.

Optrex Brand Eye Lotion (*P. Famel, Paris; Wilcox Jozeau & Co., Ltd., London*).—Extract Potentill Erect., 0.50 g.; Extr. Polyg. Bistort., 0.50 g.; Extr. Erig. Canad., 0.50 g.; Extr. Euphras. Off., 0.50 g.; Extr. Hamam. Virgin., 0.50 g.; Acid. Boric., 1.00 g.; Natr. Borac., 2.00 g.; Natr. Salicyl., 0.08 g.; Zinc. Sulf., 0.10 g.; Aq. Dist. Hamam. Virgin, Aq. Distill. ad 100.00 g.

Ovaltine (*A. Wander & Co. Ltd., London*).—Described as "composed of Malt Extract, Fresh Swiss Cow's Milk, Fresh Eggs, and converted Cocoa, and containing active Lecithin." Analysis showed Fat, 12.3%; Reducing Sugars (as Maltose), 60.0%; Nitrogenous substances calculated as Protein, 13.4%; Ash, 3.5%; Water, 1.5%.—*Brit. med. J.*, i/1910, 30.

Owbridge's Lung Tonic (*W. T. Owbridge Ltd., Hull*).—Balsam of Tolu, Oil of Aniseed and Oil of Cloves.—*Lancet*, ii/1903, 1493.

The alkaloids of Ipecacuanha were found to the amount of 0.002%. If

present in the form of Wine of the official strength this represents Ipecacuanha Wine, 15 m., and Chloroform, 2 m., in each ounce.—*Brit. med. J.*, ii/1908, 1698.

Oxien Brand Nerve Tablets (*The Giant Oxie Co. Ltd., London*).—Each tablet weighs about 18 gr. The formula is Lecithin, 0·62; Bism. Carb., 1·25; Mag. Carb. Pond., 2·50; Ferri Hypoph., 1·25; Tragacanth, 5·00; Amylum, 5·00; Acacia, 15·00; Colour, 2·92; Creta Gall., 3·33; Sucros., 60·95; Ol. Sassafras, 0·44; Ol. Gaulth., 0·28; Chirata, 0·98; Gentian 0·12; Eupatorium, 0·12; Elecampane, 0·12; Scutellaria, 0·12.

Oxien Brand Tablet Pills (*The Giant Oxie Co. Ltd., London*).—Aloin $\frac{1}{2}$ gr.; Podoph. Res., 3/20 gr.; Ext. Gentian., $\frac{1}{4}$ gr.; Camphor, 1/64 gr.; Ext. Jalap, $\frac{1}{8}$ gr.; Capsicin, 1/60 gr.; Sucrose, $\frac{1}{8}$ gr.

Panopepton (*Fairchild Bros. & Foster, New York; Burroughs Wellcome Co., London*).—100 contained Alcohol, 20; Total Solids, 26·9; Nitrogen, 1·1 (equivalent to Protein, 7·2); Ash 1·1; Sugar 7·8.—*Brit. med. J.*, ii/1909, 562.

May be dispensed by registered chemists under certain conditions.—Vol. I, p. 660.

Pazo Ointment (*Paris Medicine Co., St. Louis, Mo.; Agents: May, Robert and Co. Ltd., London*).—Zinc Oxide, 10; Camphor, 5; Carbolic Acid, 1; Balsam of Peru, 4; Ext. of Hamamelidis, 6; Yellow Beeswax, 4; Benzoated Lard, 70.—*Lancet*, i/1934, 256. (As sold in Italy.)

Penetrol Brand Inhalant (*W. B. Cartwright Ltd., Rawdon, Leeds*).—Menthol, 30·3; Ol. Lavand., 72; Ol. Cajuput, 24; Ol. Menth. Pip., 0·928; Otto Lavand., 17·7; Ol. Eucalyp., 26·25; Sp. Meth. Indus., 236.

Peps Brand Pastilles (*Peps Pastille Co., London*).—Ol. Res. Cubeb, 0·015 m.; Ol. Menth. Pip., 0·075 m.; Ol. Anisi, 0·075 m.; Ol. Eucalypt., 0·075 m. Bals. Tolut., 0·150 gr.; Ext. Pini Canad. Liq., 0·015 m.; Ext. Capsici Liq. 0·015 m.; Ext. Tussilag. Liq., 0·575 m.; Ext. Glycyrr., 2·250 m.

Perry Davis' Pain Killer (*Davis & Lawrence Co., New York*).—Spirit of Camphor, Tincture of Capsicum, Tincture of Myrrh and Alcohol.—Murrell.

Phensic Brand Tablets (*Phensic Ltd., Manchester*).—Each tablet weighs about 7 gr. The formula is Acidum Acetylsalicylicum, 46·43; Acetphenetidinum 26·57; Caffeina, 6·57; Amidopyrina, 1·79; Salicinum, 3·58; Phenylis Salicylas 0·79; Creta Gallica, 5·00; Amylum Zea Mays, 6·42; P. Acaciæ Gummi, 2·62; Ol. Limonis, 0·23.

Phosferine Brand Tonic (*Phosferine (Ashton & Parsons) Ltd., London*).—Cinchonin, Sulph., 0·028; Cinchonidin. Sulph., 0·028; Quinidin. Sulph. 0·028; Ac. Phos. Conc., 8·281; Quinin. Sulph., 0·455; Aq. Dest., 84·899; Ac. Glycerophos., 0·056; Spt. Rectif., 6·0; Sacchar. Ust., 0·225.

Phyllosan Brand Tablets (*Natural Chemicals Ltd., London*).—Chlorophyll 0·01; Phosph. Fer., 0·008; Phosph. Cal., 0·06; "Saccharose ad."

Chlorophyll contains no iron in itself but bears some close relation to iron, for it cannot be formed in a plant from which iron is excluded. It contains Magnesium, and perhaps this supplies to the component parts of Chlorophyll the same cement which iron is said to give to the hæmoglobin molecule. Phyllosan porphyrin $C_{16}H_{18}N_2O$, one of the decomposition products of Chlorophyll, has a close relationship to Hæmatoporphyrin $C_{16}H_{18}N_2O_3$, an iron-free decomposition product of Hæmoglobin. Going a stage further, Hæmopyrrol $C_8H_{13}N$ can be obtained from both. Bürgi claims that Chlorophyll may be used to aid Hæmoglobin production in the body. It is shown that we get better results from our iron pill and fresh vegetables than from Hæmoglobin preparations. In only one vegetable is Chlorophyll available in large quantities, namely spinach, and even in this it is thought to be so held up in the plant as to be not readily available for man.—*Lancet*, i/1922, 23, 90.

Pineate Brand Honey Syrup (*Bismag Ltd., London*).—Honey, 28%; Syr. Squills, 31%; Glycerine, 7%; Syr. Tolu, 32%; Oil of Pine, 0·9%; Ext. Ipecac 0·5%; Menthol, 0·1%; Oil of Peppermint, 0·5%.

Pinkettes Brand Laxative Pills (*The Dr. Williams Medicine Co., London*).—Freed from coating, each pill weighs about $\frac{1}{2}$ gr. The formula is Aloin, 50%; Resin. Podophylli, 6·66%; P. Ipecac., 10%; Oleoresin Zingiber, 6·66%; Excip. 26·68%.

Pinoleum Brand Inhalant (*The Pinoleum Company, New York; Chesebrough Mfg. Co., London*).—Menthol, 0·50 g.; Camphor, 0·50 g.; Ol. Eucalyptus Glob., 0·56 g.; Ol. Pini Pumilio, 1·00 g.; Ol. Cassia, 0·07 g.; Chlorophyll 0·10 g.; Liq. Petrolatum, 97·27 g.

Poslam (*Emergency Laboratories, New York*).—Analysis showed approximately Zinc Oxide, 12; Flowers of Sulphur, 8; Maize Starch, 18; Salicylic Acid,

5; Oil of Cade (?), 1.5; Oil of Birch Tar, 8; Anhydrous Lanolin, 25.5; Soft Paraffin, 25.5%.—*Brit. med. J.*, ii/1910, 1353.

Potter's Asthma Cure (*Potter & Clarke Ltd., London*).—For burning. Contains about 30% of Powdered Stramonium and 15% of Powdered Lobelia.

Pritchard's Teething and Fever Powders (*Pritchard's Ltd., Cheadle, Manchester*).—Average weight, 2.1 gr. Consist of Calomel, 47%; Antimony Oxide, 0.7%; Calcium Phosphate, 1.4%; Milk Sugar, 50.9%.—*Brit. med. J.*, i/1908, 1022.

Pylitna Brand Powders (*Pylitna Preparations, London*).—Each powder weighs about 45 gr., the formula being Pot. Nit., 1.739%; P. Pip. Cubeb., 6.956%; Glycyrrh. Gl. Cort., 17.393%; Sulphur. Sublim., 13.913%; Magnes. Cb., 13.913%; Pot. Bitart., 13.913%; Crot. Eleuter. Cort., 11.304%; Cinch. Succirub. Cort., 6.956%; G. Acaciæ, 13.913%.

Quincasca Brand Cold Cure Tablets (*Perox Ltd., London*).—Each tablet contains Quin. Sulph., $\frac{1}{2}$ gr.; Casc. Sag., $\frac{1}{2}$ gr.; Acetanilide, 1 gr.; Aloin, $\frac{1}{36}$ gr.; Podoph., $\frac{1}{36}$ gr.; Terr. Alb., $2\frac{1}{2}$ gr.; Amylum, $\frac{1}{2}$ gr.

Reudel Bath Saltrates (*Saltrates Inc.; International Chemical Co. Ltd., London*).—Magnesium Carbonate, 0.005; Calcium Carbonate, 0.005; Potassium Carbonate, 0.00125; Calcium Sulphate, 0.0025; Sodium Chloride, 0.0012; Lithium Carbonate, 0.00005; Borax, 0.10; Sodium Bicarbonate, 0.305; Sodium Carbonate, 0.50; Hydrogen Sulphide, 0.025; "Baregine," 0.025; "Oxygenated Salts," 0.03; Radio-active substances, traces; Aromatic Essence, sufficient quantity.—*Lancet*, i/1924, 256. (As sold in Italy.)

Rheumagic Brand Liniment (*Pickups Ltd., London*).— Δ^{β} . Propenyl Thiocarbamide, 1.94 parts; Oil of Melaleuca, 1.94 parts; Methyl Salicylate, 15.53 parts; Oleo-resin Capsici, 0.80 part; Oleum Nucis Moschatae, 0.47 part; Oleum Caryophylli, 0.16 part; Alcohol to 100 parts.

Roche's Embrocation (*Wm. Edwards & Sons, London*).—Olive Oil, Oil of Amber, Oil of Cloves, and Oil of Lemons.—Murrell.

According to *Lancet*, i/1924, 256.—Oil of Cloves, Oil of Amber, Oil of Lemon, of each, 15; Olive Oil, 55. (As sold in Italy.)

St. Jacob's Brand Liniment (*St. Jacob's Oil Ltd., London*).—Camphora, 7%; Mezereum, 2.5%; Phenol, 0.5%; Ol. Origanum, 3%; Ol. Terebinth., 58%; Ethyl Oxide, 11%; Ethyl Hydroxide, 15%; Aqua, 3%.

Sagradol Brand Laxative Emulsion (*The Angier Chemical Co., Boston, U.S.A.; The Angier Chemical Co. Ltd., London*).—Paraffinum, Liquidum, 50%; Cascara Sagrada, 8.5%; Sodium Benzoas, 0.25%; Saccharinum, 0.021%; Muc. Acacia, 15%; Glycerinum, C.P., 4%; Aromatici (Olei Anise, Coriander, Cassia, Methyl Salicylate), 0.025%; Aqua Destillata, q.s.

Sal Antisepticus, Huxley Brand (*Anglo-American Pharmaceutical Co. Ltd., Croydon*).—Liquor Antisept. Conc. (Thymol, Phenol, Methyl Salicylat., a.a. $1\frac{1}{2}$; Eucalyptus, Menthol, a.a. 1), 5; Phenyl Acetamide, 5; Sodii Sulphocarb., 5; Sodii Chloride Pur., 25; Acid. Borici Subt., 58; Acid Benzoici, 2.

Sanacine Brand Cough Mixture (*Phosferine (Ashton & Parsons) Ltd.*).—Tr. Cephælis. I., 0.840; Ol. Eucalypt., 0.013; Ext. Glycyrrh. Liq., 1.560; Ess. Menth. Pip., 0.130; Ess. Anisi Stell., 0.084; Ext. Piper. Nig. Liq., 0.260; Ext. Rorella Liq., 0.130; Sacch. Ust., 0.625; Ext. Vitis A. Liq., 0.520; Syrupus, to 100.

Sargol (*Sargol Ltd., London*).—"A Flesh Producer."—Analysis of the tablets (average weight 5.3 gr.) showed Zinc Phosphide, 0.7%; Lecithin, 1.9%; Calcium Hypophosphite, 12.9%; Sodium and Potassium Hypophosphites, 7.7%; Albumen (Soluble), 4.2%; Insoluble Protein (?Coagulated Albumen), 10.8%; Sugar, 18%.—*Brit. med. J.*, i/1912, 846.

The following formula is given:—Ext. Saw Palmetto, 2 gr.; Calcium Hypophosphite, $\frac{1}{2}$ gr.; Sodium Hypophosphite, $\frac{1}{2}$ gr.; Potassium Hypophosphite, $\frac{1}{2}$ gr.; Lecithin, $\frac{1}{2}$ gr.; Ext. Nux Vomica, $\frac{1}{12}$ gr.—*Lancet*, i/1920, 1275.

Scott's Brand Emulsion (*Scott & Bowne Ltd., London*).—Ol. Morrhuæ, 196 m.; Calcii and Sodii Hypophosphis, 9.25 gr.; Glycerini, 59 m.; Pulv. Trag., 2.7 gr.; Ol. Essential, 0.5 m.; Aqua, q.s. 1 oz.

Scott's (Dr.) Brand Bilious and Liver Pills (*W. Lambert & Co. Ltd., London*).—The average weight of each pill is about $2\frac{1}{4}$ gr. The formula is Aloes Soc., 16.56%; Aloes Barb., 10.94%; Rhei, 16.25%; Zingib., 13.75%; Sapo., 12.5%; Scamy Res., 20%; Glycyrr., 2.5%; Excipients, 7.5% (Ol. Caryoph., S.V.R., Aq.).

Shac (Stearn's Headache Cachets) (*Frederick Stearns & Company of Canada Ltd., Windsor, Ontario*).—Each wafer contains $\frac{1}{4}$ gr. of Caffeine and $2\frac{1}{2}$ gr. of Acetanilide.

Shadeine (Brown) (*The Shadeine Co., London*).—Pyrogallic Acid, 2.1%; Cupric Chloride (anhydrous), 1.3%; Hydrochloric Acid (B.P.), 0.3%.—*Brit. med. J.*, i/1910, 152.

Silbe Brand Tablets (*Silten Ltd., London*).—(For asthma).—Each tablet contains Ephedrine Hydrochloride, 0.025 g.; Theophylline, 0.05 g.; Calcium Benzylphthalate, 0.1 g.; Dimethylaminophenyldimethylpyrazolone, 0.1 g.; Starch to 0.3 g.

Silf Brand Obesity Tablets (*The Silf Co. Ltd., London*).—P. Ext. Fum. Vesic., $3\frac{1}{2}$ gr.; P. Rhei, $\frac{1}{32}$ gr.; P. Ext. Cas. Sag., $\frac{1}{4}$ gr.; Aloin, $\frac{1}{32}$ gr.; Acacia, Amylum, Sacch. Lact., q.s.

Singleton's Eye Ointment (*Stephen Green Ltd., London*).—Analysis showed principal ingredient was Red Mercuric Oxide, 7.4%; fatty basis contained *inter alia* about 4% beeswax.—*Secret Remedies*. The carton now bears declaration that the ointment contains 5.45% of Mercuric Oxide.

Sloan's Brand Liniment (*Dr. Earl S. Sloan, London*).—Ol. Camphor 20%; Liq. Ammon. Fort., 0.03%; Ol. Pini, 6%; Ol. Sassaf., 1.50%; Liq. Capsici (Non-Alcoholic), 33.57%; Methyl Salicyl., 2%; Ol. Terebinth. Rect., 36.90%.

Smedley's Chillie Paste (*Hirst, Brooke & Hirst Ltd., Leeds*).—Powdered Capsicum, 4; Lard, 60; Alkanet Root, 1.—*Lancet*, i/1924, 256. (As sold in Italy).

Smiler (Dr.) Brand Magnesia Compound (*Smiler Magnesia Co., London*).—Each fluid ounce contains:—Mist. Magnes. Hydroxid. B.P., 300 m.; Paraffin Liq., 120 m.; Glycerin., 36 m.; Tr. Anthem., 9.60 m.; Tr. Zingib. Fort., .33 m.; Ol. Anethi, Ol. Carui, Ol. Caryoph., Ol. Cinnamomi, a.a. .15 m.

Soliment Brand Solid Liniment (*Solidol Chemical Ltd., London*).—Ol. Terebinth., 58%; Sod. Sal., 5%; Ol. Wintergreen, 6%; Ol. Camph. Ess., 10%; Capsicum, 1%; Ol. Amber, 10%; Meth. Palmitate, 10%.

Staniform Brand Ointment (*Staniform Ltd., London*).—Methyl Stannic Iodide, 2%; Paraffin Moll., 98%.

Stannoxy (*Robert & Carriere, Paris; Anglo-French Drug Co. Ltd., London*).—*Tablets*. The average weight of each tablet is about 0.25 g. ($3\frac{3}{4}$ gr.). The formula is Tin (metal), 42.5%; Tin Oxide, 7.5%; Amylum, 37.5%; Sucros 12.5%.

Liquid.—Tin protochloride, 25%, in glycerin and water.

Glycerine.—Tin protochloride, 2%, in glycerin.

Ointment.—Tin protochloride in an emollient base.

Stedman's Teething Powders (*James H. Stedman, London*).—Average weight, 2.4 gr. The powder consists of Calomel, 29%, and Sugar of Milk, 71%. A trace of Alkaloids (not identified).—*Brit. med. J.*, ii/1908, 1022.

Steedman's Soothing Powders (*John Steedman & Co., London*).—Average weight, 2.8 gr. each. Consisted of Calomel, 27%; Sugar, 22%; Maiz Starch, 50.5%; Ash, 0.5%. Directions similar to Stedman's above.—*Brit. med. J.* ii/1908, 1022.

Tatcho (*Tatcho Laboratories Ltd., London*).—Borax, 2.7%; Glycerin, 2.5%; Quinine, 0.006%; Formaldehyde Solution (40%), 0.38%; colouring and perfume, a trace; Alcohol, 2.4%; Water to 100 by volume.—*Brit. med. J.*, i/1910, 15.

Taxol (*Laboratoires Lobica, Paris*).—Each tablet contains Poudre de muqueuse intestinale, 0.05 g.; Extrait biliaire, 0.10 g. Agar Agar, 0.05 g. Ferments Lactiques, 0.05 g.

Therapion No. 3 (*De Roos, Johnson & Co., London*).—Results indicate Camphor, 2.5; Glycerin, 24; Powdered Liquorice, 40; Calcium Glycerophosphate, 1.8; Extract of Gentian, 5; Extract of Damiana (?), 8; Alkaloid, 0.00. Water, to 100.—*Brit. med. J.*, i/1909, 32.

Thermogene Brand Medicated Wadding (*The Thermogene Co. Ltd. Hayward's Heath, Sussex*).—Impregnated with capsicum and methyl salicylate.

Thermogene Brand Vapour Rub (*The Thermogene Co. Ltd., Hayward's Heath*).—Camphor, 4.00; Menthol, 4.00; Oleores. Capsici, 0.04; Methyl. Salicylat., 18.00; Ol. Terebinthinæ, 12.00; Ol. Camph. Essent., 3.45; Ol. Caryophylli, 2.50; Ol. Cinnam. Fol., 2.00; Cineol, 2.00; "combined with a perfume Lanolin-Wax base and a trace of colouring matter to make 100.00."

Towle's Pennyroyal and Steel Pills (*E. T. Towle & Co. Ltd., Nottingham*).—Contain Dried Iron Sulphate, about 14 gr.; Capsicum, 86 gr.; Oil of Pennyroyal, 3 m.; Excipient, q.s. in 100 pills.—*Brit. med. J.*, ii/1907, 1653.

Trova Brand Ointment (*Sedways Ltd., London*).—Adeps Lanæ, 36.34%; Paraffin Moll., 36.34%; Paraffin. Dur., 9.08%; Ol. Cajuput., 9.75%; Sp. Vini Rect., 7.57%; Glycerol, 0.72%; Quinetum, 0.20%.

Ulceratum Brand Ointment (*L. North Ltd., Northampton*).—"Methol. Sal.," 1.63%; Zinci Oxid., 6.68%; Plumbi Carb., 4.45%; Phenyl. Hydras, 4.0%; Paraff. Molle, 57.67%; Adep. Lanæ Anhyd., 11.12%; Paraff. Durum, 14.45%.

Urace Brand Laxatives (*Newbery & Phillips Ltd., London*).—Phenolphthalein, 1.5 gr.; Pasta Theobromatis, 4.5 gr.

Urace Brand Rheumatic Liniment (*Newbery & Phillips Ltd., London*).—Methyl Salicyl., 4.216 decil.; Pip. Nig., 70.87 g.; "Sem. Senapis," 70.87 g.; Rad. Zingib., 28.350 g.; Flor. Anthem., 42.53 g.; Ol. Citron., 2.75 ml.; Liq. Virid., 2.5 ml.; Ind. M. Spt., 4.5459 l.

Urace Brand Rheumatism Tablets (*Newbery & Phillips Ltd., London*).—Each tablet contains Acetylsalicylic Acid, 0.13 g.; Guaiaci Res., 0.064 g.; Quin. Bisulph., 0.032 g.; Amylum, 0.016 g.; Saccharum, 0.016 g.

Urodonal (*J. L. Chatelain, Paris; Spencer & Co., London*).—Quinodiéthylène dianyl, 6 g. (Tartrate de diéthylène diamine, 0.14; Quinate de diéthylène-diamine, 0.28; Anisate de lithine, 0.14; Diméthylxanthine lithinique, 0.16; Anhydrométhylènenecitrate de hexaméthylènetétramine, 1.98; Citrate de sodium, 3.30); Méthylglyoxaluridine, 8 g. (Lactosuccinate de diéthylènediamine, 0.48; Tartrate de méthylglyoxalidine et de diméthylhexahydroparadiazine, 0.32; Formiate de sodium, 2.56; Citrate de carbamide, 4.64); Phosphate d'hexaméthylènetétramine, 8 g.; Excipient (Acide tartrique, 27.50 g.; Bicarbonate de soude, 50.50 g.).

Uzit Brand Ointment (*Uzit Manufacturing Co., York*).—Hydrarg. Ammon. Chlor., 0.01; Hydrarg. Ox. Rub., 0.01; Spt. Camph., 0.08; Spt. Vini Indust., 0.18; Adeps Benz., 0.72.

Valda Brand Pastilles (Distributors: *Wilcox, Jozeau & Co.*).—Ol. Menth. Pip., 0.3 g.; Ol. Eucalypt., 0.02 g.; "Ol. Thymo," 0.002 g.; "Ol. Terpinol," 0.002 g.; Sugar, 0.45 g.; Gum, 0.55 g.; for 100 pastilles.

Van Vleck's (Dr.) Absorptive Plasma (*The Dr. Van Vleck Co. Ltd., London*).—Formula approximately:—Powdered Galls, 6 parts; Menthol, 1 part; Crude Petroleum Jelly, to 100 parts.

Vapex Brand Inhalant (*T. Kerfoot & Co. Ltd., Bardsley Vale*).—Methylisopropylcyclohexanol, 16.18%; Methylisopropylcyclohexane 1:8-oxide, 4.70%; Spt. Lavand. B.P. '14, I.M.S., 47.00%; Bornyl Acetate, 0.4%; Spt. Menthol. B.P.C., I.M.S., 29.77%; Ol. Cinnam. Camph., 1.5%; Linalyl Acetate, 0.45%.

Varalettes (Bishop's Gout) (*Alfred Bishop Ltd., London*).—Showed presence of Lithium Citrate and a small quantity of what appeared to be Piperazine with the usual effervescing basis.—*Secret Remedies*.

Veganin Brand Tablets (*William R. Warner & Co. Ltd., London*).—Each tablet contains Ac. Acetyl Sal., 0.25 g.; Phenacetin, 0.25 g.; Cod. Phos., 0.01 g.; Excipient, 0.09 g.

Vegetine Brand Pills (*Newbery & Phillips, London*).—Barbaloin, Jalapin, Podophyllin, a.a. $\frac{1}{2}$ gr.; Gingerin, 1 m.; Ol. Menth. Pip., $\frac{1}{2}$ m.; Ext. Gentian, q.s.

Velox Rheumatic Tablets (*P. Gray, Barking*).—"Monoaceticacidester of Salicylic acid," 85.5; Lactose, 1.75; Maranta Arun., 12.75; Coloura, q.s.

Veno's Brand Lightning Cough Cure (*Veno Drug Co. Ltd., Manchester*).—Grindelia, 1.0%; Eriodictyon, 1.0%; Spt. Tenuior, 2.5%; Glycerin, 16.0%; Terpin. Hyd., 0.16%; Menthol, 0.002%; Bals. Tolu, 0.1%; Pot. Guaiacol Sulphonas, 2.5%; Aq. Chlorof. ad 100%.

Veno's Brand Seaweed Tonic (*Veno Drug Co. Ltd., Manchester*).—Ext. Cas. Sag. Liq., 12.781; Glycerol, 11.143; Tinct. Pod. Res., 0.420; Sodii Hypophos., 1.005; Ext. Chionanthus Vir., 1.497; Ext. Fucus Ves., 1.556; Tri-Chlor-Methane, 0.376; Aq. Destill., 81.222.

Vick Brand Vapour-Rub (*Newbery & Phillips Ltd., London*).—Camphor, 6.0 g.; Menthol, 2.0 g.; Oil of Turpentine, 5.0 ml.; Oil of Eucalyptus, 1.0 ml.; Oil of Cedarleaf, 1.0 ml.; Oil of Nutmeg, 1.0 ml.; Oil of Thyme, 1.0 ml.; Oil of Pumilio Pine, 1.0 ml.; Oleoresin of Capsicum, 0.05 g.; Guaiacol, 0.01 g.; Balsam of Peru, 0.05 g.; Petrolatum, to 100 g.

Vick-Vatronal Brand Nasal Medicament (*Newbery & Phillips Ltd., London*).—Menthol, 0.9%; Camphor, 0.3%; Eucalyptol, 1%; Methyl Salicylate, 0.2%; Oil of Nutmeg, 0.2%; Oil of Cedar Leaf, 0.1%; Liquid Petrolatum, 97.3%.

Vikelp Brand Body Building Tablets (*Health Products Laboratories, London*).—Each tablet weighs about 15 $\frac{1}{2}$ gr., the formula being Macrocytis Pyrifera (Kelp), 49.323%; Maltum, 41.400%; Chocolate, 7.200%; Gum Acacia, 1.480%; Saccharine, 0.125%; Vanillin, 0.222%; Stearic Acid, 0.250%.

Virol (*Virol Ltd., London*).—Analysis showed it to contain Fat, 12·3%; Reducing Sugars (as Maltose), 59%; Diastatic power, nil.—*Brit. med. J.* i/1910, 29.

Vitæ-Ore (*Theo. Noel Co. Ltd., London*).—According to analysis each dose would contain Ferric Oxysulphate, 0·47 gr., and Magnesium Sulphate Anhydrous, 0·15 gr.—*Brit. med. J.*, i/1911, 27.

W-5 Brand Tablets (*Gelty Distributing Co. (Ellentee Ltd.), London*).—(*For the regeneration of the skin*).—Separate packages are supplied for men and women. The following is the formula of the tablets for women.—“Novopithel, 0·025; Gonad Extr., 0·1; Ferr. Lactate, 0·125; Calcium Lactate, 0·125; Sacchar. Alb., 0·093.

Warner's Safe Cure (*H. H. Warner & Co. Ltd., London*).—Potassium Nitrate (about 10 gr. to the ounce) and various diuretic herbs.—*Lancet*, ii/1908, 1493. A mixture made with Potassium Nitrate, 50 gr.; Alcohol, 5 drachms; Gaultheria Oil, $\frac{1}{2}$ m.; Liquid Extract of Taraxacum, 10 drachms; Glycerin, 4 drachms; and Water to 8 oz. is almost identical.—*Brit. med. J.*, i/1907, 213. An Extract of Liverwort Leaves 30; Nitre, 15; Glycerin, 45; Alcohol, 60; with some Wintergreen Oil. Pills.—Aloes, Soap, Marshmallow, and Liquorice.—*Brit. Med. J.*, ii/1908, 1377.

See also formula presented to German Government authorities by manufacturer.—*Med. Pr.*, Sept. 29, 1909, 347.

Webster (Professor) Brand Susquehanna Pills (*Nottingham Botanical Institute, Nottingham*).—The average weight of each pill is about $2\frac{1}{2}$ gr. The formula is Rhei Rhizoma, 40%; Aloe Curaçao, 30%; Commiphora Myrrha, 20%; Sodii Oleas, 10%; Saccharum Fæcis, quant. suff.

Welch's Female Pills (*C. & G. Kearsley, London*).—(*Kearsley's original Widow Welch's Female Pills*).—Contain Iron Sulphate, Sulphur, Liquorice and Turmeric, with Excipient.—*Brit. med. J.*, ii/1907, 1654.

Whelpton's Purifying Pills (*G. Whelpton & Sons Ltd., Hemel Hempstead*).—Weight $2\frac{1}{2}$ gr. Examination showed Aloes (apparently Socotrine), Powdered Colocynth, Ginger and Gentian. No evidence of Mercury or Calomel.—*Brit. med. J.*, i/1911, 1326.

White Tar Brand Ointment (*Tillott's Laboratories, Westminster*).—Adeps. Lanæ Hyd., 39·3%; Paraf. Molle, 46·7%; Lana Philosophica, 10%; Metadihydroxy-benzol, 4%; Hydroxytoluene Com., 0·002%.

Williams (Dr.) Brand Pink Pills for Pale People (*The Dr. Williams Medicine Co., London*).—Freed from coating the average weight of each pill is about 3 gr. The formula is Ferri Sulph., 26·66%; Sodii Carb., 26·66%; Aloe Ferox, 2·66%; Mang. Diox., 1·77%; Zinci Phosphid., 0·16%; Cupri Sulph., 0·08%; Ext. Gent., 3·33%; Excip., 38·68%.

Winslow's (Mrs.) Syrup (*Curtis & Perkins, New York*).—Is stated to contain Senna, Sodium Citrate, Fennel, Sodium Bicarbonate, Rhubarb, Caraway, Oil of Anise, Coriander, Glycerine and Sugar Syrup.

Woodcock's Wind Pills (*Page Woodcock Ltd., London*).—Freed from coating the average weight of each pill was 1·6 gr. Evidence of the presence of Aloe (Barbados) or a preparation of Aloes, a little Ginger, a little Soap, a trace of Capsicum and Oils of Peppermint and Cinnamon and some indistinguishable vegetable tissue.—*Brit. med. J.*, i/1911, 1326.

Wooldridge Brand Gout and Rheumatic Tincture (*Wooldridge Medicine Co. Ltd., London*).—Colchicine, 0·07; Pot. Acet., 4·00; Pot. Bicarb., 4·00; Pot. Iodid, 2·00; Caramel, 0·80; Proof Spirit, 38·00; Aqua ad 100.

Yeast-Vite Brand Tablets (*Irving's Yeast-Vite Ltd., Watford*).—Each tablet weighs about 6 gr. The formula is Saccharomyces cerevisiæ, 38·39; Phenyl Semicarbazide, 8·93; Acetphenetidin, 6·25; Potassii Bromidum, 3·57; Sodii Bicarbonas, 39·29; “Amonii” Bromidum, 2·68; Caryophylli, 0·89.

These tablets formerly contained Amidopyrine and no Phenyl Semicarbazide.

Zam-Buk Brand Ointment (*C. E. Fulford Ltd., Leeds*).—Resin. Pin. Palust., 14·40%; Paraffin Dur., 21·50%; Paraffin Molle, 53·40%; Ol. Eucalypti Globul., 7·56%; Flor. Camphoræ, 1·85%; Ol. Thymi Vulgar., 0·93%; Ext. Chorophylli, 0·03%; Ol. Sassaf. Officin., 0·33%.

Zotos (*Sangers Ltd., London*).—Capsules (sea sickness preventive), contained 6·3 gr. pinkish powder consisting of 76·9% Chlorbutol and 23% Lactose.—*Brit. med. J.*, ii/1909, 1419.

Zox Powders (*The Zox Manufacturing Co., Ltd., London*).—Average weight $4\frac{1}{2}$ gr. Consists of Acetanilide only.—*Brit. med. J.*, ii/1908, 1112.

GLOSSARIES

ARABIC GLOSSARY

NOTE.—This was compiled by W. R. Robb while serving with H.M. Forces during the war, from the language actually spoken in the Tigris Valley, and differs slightly from that spoken in Syria and Egypt. It might therefore be termed pure Mesopotamian. The Glossary was subsequently amended and extended by H. C. Sinderson, Physician to the New General Hospital, Baghdad.

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|---|---------------------------------------|
| <i>Aboo Sufar</i> , jaundice. | <i>Ighma</i> , faint. |
| <i>Aboo Zowwa</i> , cholera. | <i>Iridje</i> , vein. |
| <i>Adalah</i> , muscle. | <i>Irr</i> , penis. |
| <i>Adwa</i> , contagion. | <i>Ishal</i> , diarrhœa. |
| <i>Adhwawi</i> , jackal bite. | <i>Itches</i> , elbow. |
| <i>Akab</i> , heel. | <i>Ithin</i> , ear. |
| <i>Akrash</i> , dumb. | <i>Jidam</i> , foot. |
| <i>Amee</i> , blind. | <i>Jidiri</i> , small pox. |
| <i>Araj</i> , lame. | <i>Jifn</i> , eyelid. |
| <i>Asab</i> , nerve. | <i>Jild</i> , skin. |
| <i>Athm</i> , bones. | <i>Jimah</i> , fist. |
| <i>Atrash</i> , deaf. | <i>Jised</i> , body. |
| <i>Bahim</i> , thumb. | <i>Jurra</i> , wound. |
| <i>Baydh</i> , testicles. | <i>Kabath</i> , constipation. |
| <i>Bug</i> , mosquito. | <i>Kanakina</i> , quinine. |
| <i>Buttin</i> , abdomen. | <i>Kebed</i> , liver. |
| <i>Cashuggar</i> , spoon. | <i>Kessr</i> , fracture. |
| <i>Chab</i> , ankle. | <i>Khastakhana</i> , hospital. |
| <i>Chef</i> , palm. | <i>Khedma</i> , bruise. |
| <i>Chud</i> , cheek. | <i>Kilwa</i> , kidney. |
| <i>Dam</i> , blood. | <i>Kitif</i> , shoulder. |
| <i>Demboos</i> , pin. | <i>Lesha</i> , dead body. |
| <i>Dihn</i> , oil. | <i>Lissan</i> , tongue. |
| <i>Dihn Zait</i> , olive oil. | <i>Ma-ada</i> , stomach. |
| <i>Dihn Kharwa</i> , castor oil. | <i>Machloob</i> , hydrophobia. |
| <i>Dimagh</i> , brain. | <i>Mai</i> , water. |
| <i>Dowa</i> , medicine. | <i>Madjrook</i> , wounded. |
| <i>Dra</i> , arm. | <i>Magnoon</i> , insane. |
| <i>Dukk</i> , phthisis. | <i>Maljeedoo</i> , arm sling. |
| <i>Dumbla</i> , sore. | <i>Mardh</i> , illness. |
| <i>Ejzachi</i> , chemist. | <i>Marham</i> , ointment. |
| - <i>Ek</i> or - <i>tek</i> as a suffix signifies "your." | <i>Masareen</i> , bowels. |
| Thus "Hazurtek" means "your side." | <i>Masmoom</i> , poisonous. |
| <i>Eyein</i> , eye. | <i>Middah</i> , pus. |
| <i>Fachud</i> , hip. | <i>Mitchloob</i> , hydrophobia. |
| <i>Firash</i> , bed. | <i>Nafas</i> , breath. |
| <i>Frengi</i> , syphilis. | <i>Nezhla</i> , catarrh. |
| <i>Gacha</i> , cough. | <i>Racheta</i> , prescription. |
| <i>Galub</i> , heart. | <i>Rass</i> , head. |
| <i>Gharghara</i> , gargle. | <i>Ridjla</i> , leg. |
| <i>Goosa</i> , forehead. | <i>Rimsh</i> , eyelash. |
| <i>Hab</i> , pill or tablet. | <i>Rookoboy</i> , knee. |
| <i>Hajib</i> , eyebrow. | <i>Rugba</i> , neck. |
| <i>Hakeem</i> , doctor. | <i>Rusook</i> , wrist. |
| <i>Halk</i> , mouth. | <i>Safra</i> , bilious. |
| <i>Harq</i> , burn. | <i>Saheyah</i> , sanitary department. |
| <i>Hasbah</i> , measles. | <i>Sayarat-es-sahha</i> , ambulance. |
| <i>Hasura</i> , side. | <i>Schoona</i> , fever. |
| <i>Hazurtek</i> , your side. | <i>Schtadt</i> , bandage. |
| <i>Henitch</i> , chin. | <i>Shar</i> , hair. |
| <i>Ichasm</i> , nose. | <i>Sheesha</i> , bottle. |
| <i>Id</i> , hand. | <i>Shiffaf</i> , lips. |
| | <i>Shrunka</i> , syringe. |

Arabic Glossary—*continued*

Simm, poison.
Sin, tooth.
Soof, wool.
Spirtoo, methylated spirit.
Sudra, chest.
Susanak, gonorrhœa.
Taharl, spleen.
Tenteryoke, tincture of iodine.
Thahr, back.
Toze, powder.
Ukhut, Baghdad boil (oriental sore).
Uja, pain.

Urther, finger nail.
Usbah, finger.
Usbah ridjla, toe.
Waja rass, headache.
Warram, swelling.
Widja, face.
Yimina, right hand.
Yissira, left hand.
Yukos, cut.
Zerdoom, throat.
Zibb, penis.
Zowwa, vomit.

BELGIAN GLOSSARY

Belgian prescriptions are written in Latin or French (vide French Glossary) or a mixture of both languages. For a note on Belgian prescriptions by V. Renneboog, see *Chem. & Drugg.*, i/1915, 362.

DANISH GLOSSARY

Aandedrag, breathing.
Aare, vein.
Aare-Indsprøjtning, intravenous injection.
Atomsprøjte, spray or atomiser.
Badevand, lotion (lit. bath water).
Badning, fomentation.
Blære, blister.
Blandes, to be mixed.
Belægges (Piller), to be coated (pills).
Børstes, to be brushed.
Brækmiddel, emetic.
Citronsaft, lemon juice.
Daglig, daily.
Den smærtefulde Del, the painful part.
Dessertskefuld, dessertspoonful.
Draaber, drops.
Døgnet, the space of 24 hours.
Efter Maaltid, after meals.
Etiket med Anvisning, label with formula.
Flaske, bottle.
Forkølelse, cold.
Forsølves (Piller) to be coated (pills).
Fortyndes, to be diluted.
For udvortes Brug, for external use.
Før Maaltid, before meals.
Gift, poison.
Glas Kapsler eller smaa Flasker, glass capsules or ampoules.
Gnidning, friction.
Gummerne, the gums.
Gurglevand, gargle.
Haarvand, hair-lotion.
Hjærte, heart.
Hostemixtur, cough-mixture.
Hovedpine, head-ache.
Hud-Indsprøjtning, subcutaneous injection.
Hver anden, every two.

Hver tredje, every three.
Igle, leech.
Ikke, not.
I lige Dele, of each equal parts.
Indaanding-indauder, inhalation inhaler.
Indgnid, rub.
Indgnides, to be rubbed.
Indgydes, to be instilled.
Indsprøjtes, to be injected.
Indsprøjtning, injection.
I Vægt, by weight.
Klystér, enema.
Knuses eller brækkes, to be crushed or broken.
Kop, cup.
Krukke, pot.
Latverge, electuary.
Lige Dele, equal parts.
Ligtorn, corn.
Mælk, milk.
Mellem, between.
Moderkrans, pessary.
Mundvand, mouth-wash.
Muskel-Indsprøjtning, intramuscular injection.
Nat, night.
Næse, nose.
Næsebor, nostrils.
Omrystes, shake (the bottle).
Omslag, poultice.
Opblæsning, flatulence.
Opløse, dissolve.
Opsnuses gennem Næseborene, to be sniffed up the nostrils.
Pensle, paint (lit. pencil).
Pensles, to be painted.
Rystes, shake (the bottle).
Signatur, label (medical label).
Skefuld, spoonful.

Danish Glossary—continued

Smærte, pain.
Som foreskrevet, as directed.
Spiseskefuld, tablespoonful.
Sprøjte, syringe.
Stikpille, suppository.
Straks, at once.
Tages, to be taken.
Tandmiddel, dentifrice.
Teskefuld, teaspoonful.
To Gange, twice.
Tre Gange, three times.

Ved Sengetid, just before retiring to rest (lit. at bed-time).
Vekselvis, alternately.
Vægt, weight.
Øjendraaber, eye-drops.
Øjelaag, eye-lids.
Øjenhaar, eye-lashes.
Øjenskaerm, eye-shade.
Øjenvand, eye-wash.
Ørepine, ear-ache.

DUTCH GLOSSARY

Ademhaling, breathing.
Ader, vein.
Bedekken (pillen), to be coated (pills).
Besproeiingstoestel, atomiser or spray.
Bestrijken, to be painted.
Blaar, blister.
Baarmoederkrans, pessary.
Braking, vomiting.
Citroensap, lemon juice.
Dagelijks, daily.
De flesch, bottle.
Dicht bij, near to.
Den volgende morgen, the next, or following morning.
Droppels or druppels, drops.
Etiket met recept, label with formula.
Gebruik, use, application.
Gedurende het bruisen, during effervescence.
Gegruisd of in stukjes gebroken, to be crushed or broken.
Gelijke deelen, equal parts.
Glazen capsules, glass capsules or ampoules.
Glazen staafje, glass rod.
Goedschudden, to be well shaken (the bottle).
Gorgelen, gargle.
Het pijnlijk deel, the painful part.
Het tandvleesch, the gums.
Hoest, de, the cough.
Inademing-respirateur, Inhalation-inhaler.
Indien het hoesten lastig is, when the cough is troublesome.
Indruppelen, to be instilled.
Inspuiting binnen de spieren, intramuscular injection.
Inspuiting binnen de aderen, intravenous injection.
Inspuiting onder de huid, subcutaneous injection.
Klister spuit, enema.
Kokend, boiling.
Kopje, cup.
Melk, milk.
Met mate, moderately.
Mondspoeling, mouth-wash.

Na den maaltijd, after meals.
Neertiggende (rustende), lying down.
Niet te gebruiken, not to be taken.
Om de beurt, alternately.
Om op te snuiven, to be sniffed up the nostrils.
Onmiddellijk, immediately.
Ooghaartjes, eye-lashes.
Oogkapje, eye-shade.
Oogleden, eye-lids.
Oogwassching, eye-wash.
Ook, also.
Op de gebruikelijke wijze, in the usual manner (as taken before).
Papmiddel, fomentation.
Per gewicht, by weight.
Plaatselijk aan te wenden, for local use only.
Potje, pot.
Prikkelend, irritable.
Purgeerend stroopje, electuary.
Spoeling voor de oogen, eye-wash.
Sproeier, spray.
Spuut, syringe.
Steekpilletje, suppository.
Stopvel van bluksel, tampon.
Tabletje, tablet.
Tandpoeder, dentifrice.
Van elk evenveel, of each equal parts.
Verdeeld in gelijke deelen, let it be divided into equal parts.
Vergift, poison.
Verzilveren (pillen), to be silvered (pills).
Volgens het voorschrift, as directed.
Voor het naar bed gaan, just before retiring to rest.
Voor inspuiting, to be injected.
Voor inwendig gebruik, for internal use.
Voor uitwendig gebruik, for external use.
Waskaars, bougie.
Winderigheid, flatulence.
Wrijven, rub.
Wrijving, friction.
Zonder, without.
Zoo noodig, if necessary.

FRENCH GLOSSARY

- A argenter (pilules)*, to be silvered (pills).
A baisse-langue, tongue-depressor.
A broyer ou concasser, to be crushed or broken.
A dragéfier (pilules), to be coated (pills).
A être instillé, to be instilled.
A moins que, unless.
Ampoule, blister.
Après les repas, after meals.
Au-dessus, above.
Au poids, by weight.
Avant les repas, before meals.
Baguette en verre, glass rod.
Bande, a bandage.
Bandage, a truss.
Biberette, feeding cup.
Bien, well.
Bien agiter le flacon, the bottle to be well shaken.
Boire, drink.
Bougie, a catheter.
Bouillant, boiling.
C.à.c., à.d., à.s. = cuillerée à café, à dessert, à soupe, *q.v.*
Chaque jour, daily.
Charpie, lint.
Chauffé, warmed.
Cils, eye-lashes.
Cœur (le), the heart.
Collyre, eye-wash.
Comme il a été prescrit, as directed.
Compte-gouttes, a small glass tube to count drops.
Coqueluche, whooping cough.
Coricide, corn solvent.
Coton hydrophile, absorbent wool.
Crépine et pulvérisateur, spray and atomiser.
Cuillerée, spoonful.
Cuillerée à café, teaspoonful.
Cuillerée à dessert, dessert-spoonful (10 g.).
Cuillerée à soupe, tablespoonful.
Cuillerée à thé, teaspoonful (ou à café—5 g.).
Cuillerée ordinaire, tablespoonful (15 g.).
Cuir, leather.
De bonne heure demain, early to-morrow.
De jour en jour, from day to day.
De la façon habituelle, in the usual manner.
De la façon prescrite, in the manner directed.
Demain matin, to-morrow morning.
Demain soir, to-morrow night.
Demis, dislocated.
De temps en temps, occasionally.
D'h. en h. (D'heure en heure), every hour.
Dissoudre, dissolve.
Doigtier, a finger stall.
Douleur, pain.
Dover Poudre, Dover's Powder.
Drap d'hôpital, waterproof sheeting.
Droite (à), to the right.
Ds. (Dans), in.
Enème, enema.
En se couchant, on going to bed.
En se levant, on getting up.
Ensemble, together.
Entre, between.
Etiquette, slip-label.
Etiquette avec formule, label with formula.
Flacon, bottle.
Flacon (le) ayant été agité, the bottle having been shaken.
Flatulences, flatulence.
Fomentation, fomentation.
Foulé, sprained.
Garde-vue, eye-shade.
Gargariser, gargle.
Gencives (les), the gums.
Gouttes, drops.
Hier, yesterday.
Humburgum, opium.
In caps. amyl, in cachets.
Inhalation-inhalateur, inhalation-inhaler.
Injecteur, syringe.
Injection intramusculaire, intramuscular injection.
Injection intraveineuse, intravenous injection.
Jus de citron, lemon juice.
Jusqu'à ce que, up to.
Juste avant d'aller se coucher, just before retiring to rest.
La hanche, the hip.
Lait, milk.
Main (la), the hand.
Le (or la) même, the same.
Mechoachon, jalap.
Ne pas avaler, not to be taken.
Nuit, night.
Oeillère, eye-cup.
Ouate, cotton wool.
Pansements, dressings.
Par degrés, by degrees.
Passe-partout, an address label.
Paupières, eye-lids.
Pendant l'effervescence, during effervescence.
Pendant que la douleur dure, while the pain lasts.
Poignée, handful.
Pour être appliqué avec la brosse, to be brushed.
Pour être appliqué avec le pinceau, to be painted.
Pour être aspiré par les narines, to be sniffed up the nose.

French Glossary—continued.

Pour être injecté, to be injected.
Pour l'usage partiel seulement, for local use only.
Pour placer dans l'oeil, to be placed in the eye.
Pour usage extérieur, for external use.
Pr. (Pour), for.
Près de, near to.
Quand la toux est gênante, when the cough is troublesome.
Rince-bouche, mouth-wash.
Sangsue, leech.
Sans, without.
Saturne, lead.
Semaine, week.
Seul, alone.
Si nécessaire, if necessary.
Spasmodrap, adhesive plaster.
Tamiser, to sift.
Tarlatane, muslin.
Tasse, cup.

Timbre à ordonnances, prescription stamp.
Tout les deux jours, every other day.
Tous les matins (soirs), every morning (night).
Tous les quarts d'heure, every quarter hour.
Tous les trois jours, every third day.
Toutes les deux heures, every two hours, or every other hour.
Trouble, turbid.
Toux (la), the cough.
Un blanc d'oeuf, white of an egg.
Une fois, once.
Un jaune d'oeuf, yolk of an egg.
Veine, vein.
Verre à madère, wineglass.
Verrée (une), wineglass (8 *cuillerées ordinaires*—120 g.).
Versez, pour off.
Vessic à glace, ice-bag.

GERMAN GLOSSARY

Abend, evening.
Abkochung, decoction.
Abwechselnd, alternately.
Ader, vein.
Alle - Stunden - Tropfen zu nehmen, so many drops every - hours.
Alle viertel Stunden, every quarter-hour.
Alle zwei Stunden, every other hour.
Allmählich, by degrees.
Anwenden, apply.
Atmen, breathing.
Auflösen, dissolve.
Augenlider, eye-lids.
Augenschirm, eye-shade.
Augenwasser, eye-wash.
Augenwimpern, eye-lashes.
Ausgenommen wenn, unless.
Ausgiessen, pour off.
Ausserlich anzuwenden, for external use.
Bahung, fomentation.
Becher, a cup.
Beim zu Bett gehen, at bedtime.
Bis auf, up to.
Blähung, flatulence.
Blutegel, leech.
Brandblase, blister from burn or scald.
Bürsten, to be brushed.
Charpie-Bausch, tampon.
Der schmerzende Teil, the painful part.
Dasselbe, the same.
Dessertlöffel, dessertspoonful.
Diese Arznei darf nicht eingenommen werden, not to be taken.
Diese Arznei darf ohne erneute schriftliche Verordnung des Arztes nicht repetiert werden, this medicine may not be repeated without written order of the physician.
Dragieren (pillen), to be coated (pills).

Drei mal täglich, thrice daily.
Durch die Nase einzuziehen, to be sniffed up the nostrils.
Ebenfalls, also.
Eigelb, yolk of an egg.
Eingeben, administer.
Einspritzung, injection.
Einspritzung in die Adern, intra-venous injection.
Einspritzung in die Muskeln, intra-muscular injection.
Einspritzung unter die Haut, sub-cutaneous injection.
Einzuspritzen, to be injected.
Einzutropfeln, to be instilled.
Eiweiss, white of an egg.
Erbrechen, vomiting.
Erwarmen, to be warmed.
Esslöffel, tablespoon.
Etikette mit Rezept, label with formula.
Eventuell, idiomatic word now very popular in German. May mean, "if possible" or "possibly" or "for example."
Flasche, bottle.
Frottieren, friction.
Für innerlichen Gebrauch, for internal use.
Gelegentlich, occasionally.
Genau, accurately.
Genugend, sufficiently.
Gestern, yesterday.
Gift, poison.
Glaskapsel oder Phiole, glass capsule or ampoule.
Glasstab, glass rod.
Gleiche Teile, equal parts.
Gargelwasser, gargle.
Gut, well.

German Glossary—continued.*Herz*, heart.*Hüfte*, hip.*Husten*, cough.*In das Auge zi bringen*, to be placed in the eye.*In der angegebenen Weise*, in the manner directed.*In der gewohnten Weise*, in the usual manner.*In gleiche Teile zu teilen*, to be divided into equal parts.*Inhalations-Apparat*, inhaler.*Jeden Abend*, every evening.*Jeden Morgen*, every morning.*Jeden zweiten Tag*, every other day.*Klystier*, enema.*Kochend*, boiling.*Kurz vor dem Schlafengehen*, just before retiring to rest.*Leder*, leather.*Löffel*, spoon.*Mazerieren*, macerate.*Messerspitze voll*, as much as lies on the point of a knife.*Morgen früh*, tomorrow morning.*Mundwasser*, mouth-wash.*Mutterzapfen*, pessary.*Nach Anweisung*, as directed.*Nach Bedarf*, when required.*Nach dem Essen*, after meals.*Nachdem man die Flasche umgeschüttelt hat*, the bottle having been first shaken.*Nach einer Stunde*, at the expiration of an hour.*Nach Gewicht*, by weight.*Nahe*, near.*Niederliegen*, lying down.*Nur auf ärztliche Anweisung abzugeben*, to be given only on the medical man's direction.*Nur für äußerlichen Gebrauch*, for external use only.*Nur für örtlichen Gebrauch*, for local use only.*Ohne*, without.*Pinselfeln*, to be painted.*Recht*, right.*Reiben*, rub.*Reizbar*, irritable.*Schmerz*, pain.*Sofort*, immediately.*So lange der Schmerz anhält*, while pain lasts.*Spritze*, syringe.*Stets kühl zu halten*, to be kept cool.*Streichen*, spread.*Stuhlzapfchen*, suppository.*Stunde (Eine)*, one hour.*Tafelchen*, tablet.*Täglich*, daily.*Theelöffel*, teaspoonful.*Topf*, pot.*Trunk*, draught.*Ueber*, above.*Uebersilbern (Pille)*, to be silvered (p).*Umschütteln*, to shake (the bottle).*Verbandwatte*, absorbent wool.*Verordnen*, prescribe.*Von Tag zu Tag*, from day to day.*Vor dem Gebrauch gut umzuschütteln*, to be well shaken before use.*Vorsicht*, with care.*Vorsichtig*, cautiously.*Während des Aufbrausens*, during effervescence.*Wenn der Husten belästigt*, when cough is troublesome.*Woche (Eine)*, one week.*Zahnfliesch*, the gums.*Zahnreinigungsmittel*, dentifrice.*Zerreiben oder zerbrechen*, to crushed or broken.*Zerstäubungs-Apparat*, spray or atomiser.*Zitronensaft*, lemon juice.*Zubereitet*, prepared.*Zu gleichen Teilen*, of each equal part.*Zu nehmen*, to take.*Zwischen*, between.**ITALIAN GLOSSARY***A caldo*, warmed.*A essere aspirato dalle narici*, to be sniffed up the nostrils.*A frantumarsi o spezzarsi*, to be crushed or broken.*Aggiungere un cucchiaino ad un mezzo litro di acqua bollente, e fare inalazioni colla evaporazione*, one teaspoonful to a "pint" of boiling water and the steam inhaled.*Agitare la bottiglia avanti l'uso*, the bottle having been first shaken.*A gradi*, by degrees.*A ldi sopra*, above.*A meno che*, unless.*A peso*, by weight.*Apparecchio respiratorio*, respirator.*Applicare con un pennello*, to brush.*Applicare la filaccia sulla ferita frequentemente e appena asciutta, e ripetere di nuovo l'applicazione*, apply lint to the wound frequently and as soon as dry repeat the application again.*Bacchetta d vetro*, glass rod.*Bollire*, boiling.*Bottiglia*, bottle.

Italian Glossary—continued.

Candela, bougie.
Capsule o ampolle di vetro, glass capsules or ampoules.
Ciglia, eye-lashes.
Clistere, enema.
Collirio, eye-wash.
Come fu detto, as directed.
Come fu detto avanti, as previously directed.
Cucchiano da caffè, dessertspoon (very few people take "tea" in Italy).
Cucchiaino, spoonful.
Cucchiaino da tavola, tablespoonful.
Cuoio, leather.
Da applicarsi dietro l'orecchio destro, apply behind the right ear.
Da applicarsi eggermente prima di coricarsi, to be applied lightly at bedtime.
Da applicarsi sulla eruzione cutanea, to be applied to the eczematous rash.
Da argentarsi (pillole), to be silvered (pills).
Da bere, drink.
Da instillarsi, to be instilled.
Da ricoprirsi (pillole), to be coated (pills).
Da sciogliersi, dissolve.
Da somministrarsi, to be administered.
Da strofinarsi con un panno sul cuoio cappelluto sera e mattina, to be rubbed into the bare patch on the scalp night and morning.
Da usarsi localmente, for local use only.
Da vicino, near to.
Di giorno in giorno, from day to day.
Diviso in parti uguali, of each equal parts.
Dolore, pain.
Domani sera, tomorrow night.
Domattina, tomorrow morning.
Domattina presto, early tomorrow.
Dopo i pasti, after meals.
Dopo un'ora, at the expiration of an hour.
Esattamente, accurately.
Etichetta, label.
Etichetta con formula, label with formula.
Falaccia, lint.
Filtrare, strain.
Fino a, up to.
Fino a che dura il dolore, while the pain lasts.
Fra mezzo, between.
Frizioni, friction.
Gargarizzare, gargle.
Giacere, lying down.
Giornalmente, daily.
Giusto, right.
Gocce, drops (of liquid).
Idrofilo, absorbent.

Ieri, yesterday.
Il cuore, the heart.
Inalazioni-inalatore, inhalation inhaler.
Iniezione sottocutenea, subcutaneous injection.
Insieme, together.
L'anca, the hip.
La mano, the hand.
La tosse, the cough.
Latte, milk.
Le gengive, the gums.
Lo stisso, the same.
Non piu di 4 volte al giorno, not more than four times a day.
Ogni due ore, *Un'ora si e l'altra no*, every other hour.
Ogni quarto d'ora, every quarter of an hour.
Ogni sera, every night.
Ogni due ore, every two hours.
Ogni tre giorni, every third day.
Palpebre, eye-lids.
Pastiglie, lozenges.
Pennellare la gola ogni giorno, una mezz'ora dopo colazione, paint the throat every day about half an hour after breakfast.
Per iniezioni, to be injected.
Per pennellature, to be painted.
Per pennellature alle narici due volte al giorno, apply to the nostrils with a camel's hair brush twice a day.
Per sciacquare la bocca, mouth-wash.
Prima di coricarsi, just before retiring to rest.
Pure, also.
Quando la tosse arreca disturbo, when the cough is troublesome.
Sera, night.
Se sara necessario, if necessary.
Settimanalmente, weekly.
Senza, without.
Siringa, syringe.
Sorso, draught.
Spruzzatore, spray.
Stoppaccio, tampon.
Strofinare, rub.
Sugo di limone, lemon juice.
Tazza, cup.
Tre volte al giorno, three times a day.
Tutte le mattine, every morning.
Una goccia dentro la pupilla degli occhi una volta al giorno, a drop into the lower lid of each eye once a day.
Una manciata, handful.
Una settimana, a week.
Una volta, once.
Un bicchiere da vino, wine-glass.
Un bianco d'uovo, white of an egg.
Un giorno si ed un giorno no, every other day.

Italian Glossary—continued.*Un taelo d'uovo*, yolk of an egg.*Un uovo*, an egg.*Vaporizzatore*, atomiser.*Vaso*, pot.*Veleno*, poison.*Vena*, vein.*Versare*, pour off.*Vescica*, blister.*Vicino*, near.*Visiera*, eye-shade.**PORTUGUESE GLOSSARY***A*, the (feminine).*Acima*, above.*Algalia*, bougie.*Almoço*, breakfast.*Alternadamente*, alternately.*Amanhã á noite*, tomorrow night.*Amanhã pela manhã*, tomorrow morning.*A. menos que*, unless.*A parte dorida*, the painful part.*A pelle de craneo, couro (cabelludo)*, scalp.*A peso*, by weight.*Applica-se suavemente naséde da dór*, to be applied gently to the painful part.*Aquecido*, warmed.*A serem cobertas (pilulas)*, to be coated (pills).*A serum prateadas (pilulas)*, to be silvered (pills).*A ser instillado*, to be instilled.*A ser pincelado*, to be brushed.*A ser pintado*, to be painted.*As gengivas*, the gums.*Atraz*, behind.*Banho para o olho*, eye-wash.*Beber*, to drink.*Bem*, well.*Cabelludo*, hairy.*Calvo*, bald.*Capsulas ou ampoulas de vidro*, glass capsules or ampoules.*Cautelosamente*, cautiously.*Chiavena, Chicara*, cup.*Clyster*, enema.*Coár*, to strain.*Colhér cheia*, spoonful.*Colhér de chá cheia*, teaspoonful.*Colhér de doce cheia*, dessertspoonful.*Colhér de sopa cheia*, tablespoonful (soup-spoon).*Com cuidado*, cautiously, with care.*Como indicado nas instruções*, as directed.*Com preicsão*, accurately.*Coração*, of the heart.*Couro*, leather.*Cuidadosamente*, carefully.*De deitarse, á hora*, at bedtime.*De dia a dia*, from day to day.*Depois*, after.*De tres em 3 dias*, every third day.*De vez em quando*, occasionally.*Direito, lado*, right side.*Dôr*, pain.*Em partes eguaes, de cada*, of each equal parts.*Emquanto durar a dór*, while pain lasts.*Entre*, between.*Erupção*, the rash.*Esfregar*, to rub.*Estender*, to stretch, extend.*Esterilisar*, sterilise.*Etiqueta com formulario*, label with formula.*Exactamente antes de retirarse para descansar*, just before retiring.*Fios de linho, or lichino*, lint.*Flatulencia*, flatulence.*Friccionar*, rub.*Fricção*, friction.*Fomentação*, fomentation.*Garganta*, the throat.*Gargarejo*, gargle.*Garrafa, or Frasco*, bottle.*Garrafa bem agitada*, the bottle well shaken.*Gemma d'un ovo*, yolk of egg.*Gotas*, drops.*Hontem*, yesterday.*Hostia*, cachet or wafer.*Inhalação - inhalador*, inhalation, inhaler.*Injecção, intramuscular*, intramuscular injection.*Injecção intravenosa*, intravenous injection.*Injecção subcutanea (or epidermica)*, subcutaneous injection.*Irritavel*, irritable.*Lavagem de boca*, mouth-wash.*Lavagem para os olhos*, eye-wash.*Leite*, milk.*Mais*, more.*Mão cheia*, handful.*Mão*, hand.*Mesmo*, same.*Não*, not.*Noite*, night.*No meio de*, in the middle of.*O*, the (masculine).*Orelha*, ear.*Pala para o olho*, eye-shade.*Palpebras*, eye-lids.*Panella*, pot.*Para aspirar pela ventas*, to be sniffed up the nostrils.*Para ser*, to be.*Para ser injectado*, to be injected.*Para ser triturado o quebrado*, to be crushed or broken,

Portuguese Glossary—continued.

Para uso externo, for external use.
Pela manhã, in the morning.
Pellica, kid leather.
Perto (de), junto (a), near (to).
Pestanas, eye-lashes.
Pó, powder.
Pulverizador, spray and atomiser.
Quadril, hip.
Refeições, meals.
Respiração, breathing.
Respirador, respirator.
Semana, uma, a week.
Seringa, syringe.
Sítio, place.
Sem, without.
Sim, yes.
Sumo de Limão, lemon juice.
Taça, large cup (goblet, bowl).
Tambem, also.

Tampão, tampon.
Todos os dias, daily.
Tosse, cough.
Uma gota na palpebra inferior, de cada olho, uma vez por dia, a drop into the lower lid of each eye once daily.
Uma hora sim, uma não, every other hour (one hour yes, one no).
Uma vez, once.
Um dia sim outre não, every other day.
Vareta de vidro, glass rod.
Vasar, to pour off.
Veia, vein.
Veneno, poison.
Ventá, nostril.
Vesicatório, blister.
Vez, cada, each time.

SPANISH GLOSSARY

Acepisellar, to be brushed.
Agua para lavar laboca, mouth-wash.
Agua para lavar los ojos, eye-wash.
A la hora de acostarse, at bed-time.
Almuerzo, breakfast (lunch).
Alternativamente, alternately.
Ampollus de vidrio, glass ampoules.
A no ser que, unless.
Aparato de inspirar, inhaler.
Aplíquese suavemente al sitio del dolor, apply gently to the painful parts.
Aspiración, breathing.
Atrás, behind.
Beber, to drink.
Bien, well.
Cabella (el) del cráneo, the hair of the scalp.
Cabritilla, kid leather.
Cadera, hip.
Calentado, warmed.
Calvo, bald.
Candelilla, bougie.
Cápsulas de vidrio, glass capsules.
Cerca, near, near to.
Colar, to strain.
Comidas, meals.
Con cuidado, with care.
Con precisión, accurately.
Corazón el, the heart.
Cubrirse, to be coated (pills).
Cucharada, spoonful.
Cucharada de postre, dessertspoonful.
Cucharada de sopa, soup- or table-spoonful.
Cucharadita de té, teaspoonful.
Cuero, leather.
Cuidadosamente, carefully, accurately, cautiously.
De día en día, from day to day.
Derecha, right (hand).
Después, after.

De tres en tres dias, every third day.
De vez en cuando, occasionally.
Dolor, pain.
El, the (masculine).
En medio de, in the middle of.
Encías, the gums.
Encima, above.
Eutre, between.
Esterilizar, sterilise.
Exactamente antes de retirarse para dormir, just before retiring.
Extender, to spread.
Frotar, rub.
Garganta, the throat.
Giro, draft.
Gotas, drops.
Hilas de lino, lint.
Inyección entrevenoso, intravenous injection.
Inyección intramuscular, intramuscular injection.
Inyección subcutáneo, subcutaneous injection.
Jeringa, syringe.
Jugo de limón, lemon juice.
La, the (feminine).
La parte que duele, the painful part.
Leche, milk.
Llegado, arrived.
Loción, eye-wash.
Mano, hand.
Mañana, por la mañana, tomorrow morning.
Mano llena, handful.
Mañana por la noche, tomorrow night.
Más, more.
Mientras dura el dolor, while the pain lasts.
Mismo, same.
Nariz, nostril.

Spanish Glossary—continued.

No, not.

Noche, night.

Oblea, wafer.

Orden (or Pedido), order.

Oreja, ear.

Para inspirar por las narices, to be sniffed up the nostrils.

Para instilar, to be instilled.

Para inyector, to be injected.

Para ser, to be.

Para uso externo, for external use.

Párpados, eye-lids.

Partes iguales de los dos, of each equal parts.

Pestañas, eye-lashes.

Píldoras (*Mézclese y háganse 100 Píldoras*). (*Háganse* is frequently contracted to "H"), Pills (mix and prepare 100 pills).

Pintarse, to be painted.

Platearse, to be silvered (pills).

Polvo, powder.

Por la mañana, in the morning.

Potecillo, pot.

Por peso, by weight.

Restregar, to rub.

Rociador y Pulverizador, spray and atomiser.

Romperse, to be crushed or broken.
Rótulo con fórmula, label with formula.

Sanguijuela, leech.

Según se dirige, as directed.

Semana, a week.

Sin, without.

Sitio (or lugar), place.

Tambien, also.

Tapón, tampon.

Taza, cup (drinking) or tea cup.

Todos los días, daily.

Tos, cough.

Un ahora si y la otra no, every other hour.

Una gota en el párpado inferior de cada ojo, una vez al día, a drop into the lower lid of each eye once daily.

Unavez, once.

Un día sí y el otro no, every other day.

Vaciar, to pour off.

Varilla de vidrio, glass rod.

Vejigatorio, blister.

Vena, pain.

Veneno, poison.

Vez una, once (one time).

Visera, eye-shade.

Yema de huevo, yolk of egg.

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